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=> s liposome conjugate
L1          324 LIPOSOME CONJUGATE

=> s l1 and HLA-DR
L2            0 L1 AND HLA-DR

=> s HLA-DR ligand conjugate
L3            0 HLA-DR LIGAND CONJUGATE

=> s HLA-DR ligand
L4           17 HLA-DR LIGAND

=> s l1 and conjugate
L5          324 L1 AND CONJUGATE

=> s l4 and conjugate
L6            0 L4 AND CONJUGATE

=> s anti-HLA-DR liposome
L7            0 ANTI-HLA-DR LIPOSOME

=> s liposome
L8       155660 LIPOSOME

=> s l8 and targeting
L9         8975 L8 AND TARGETING

=> s l9 and HLA-DR
L10          30 L9 AND HLA-DR

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11          14 DUP REMOVE L10 (16 DUPLICATES REMOVED)

=> d l11 1-14 cbib abs

L11  ANSWER 1 OF 14  CAPLUS  COPYRIGHT 2005 ACS on STN
2005:696640   Document No. 143:199740  Onconase complex conjugated with folate
      for diagnosis and treatment of cancer, infection, cardiovascular disorder
      and autoimmune disease.  Hansen, Hans J.; McBride, William J.; Goldenberg,
      David M.; Rossi, Edmund A.; Chang, Chien-Hsing Ken (Immunomedics, Inc.,
      USA).  PCT Int. Appl. WO 2005069994 A2 20050804, 40 pp.  DESIGNATED
      STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA,
      CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
      GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
      LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH,
      PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
      UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI,
      CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE,
      NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO
      2005-US2193 20050124.  PRIORITY: US 2004-2004/PV538396 20040122.
AB    Because the folate receptor (also called the folate binding protein, FBP)
      is overexpressed on certain malignant cell types, targeting of
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the folate receptor has been proposed as a potential mechanism for delivery of drugs and/or radiopharmaceuticals to treat cancer. Onconase and/or variants with ribonucleolytic activity, such as rapLR1, present useful therapeutic mols. for preparing folate conjugates and complexes. The conjugates and complexes can be targeted to and internalized by targeted tissues. The conjugates and complexes may be formulated with a pharmaceutically acceptable excipient to form a primary therapeutic agent. The conjugates and complexes may be useful as primary therapeutic agents, which may be administered with addnl. therapeutic or diagnostic agents. Also disclosed are kits that include the conjugates and complexes.

L11 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

2005:98817 Document No. 142:183318 D-amino acid peptide conjugates in radioimmunotherapy and radiol. diagnosis. McBride, William J.; Goldenberg, David M. (Immunomedics, Inc., USA). U.S. Pat. Appl. Publ. US 2005025709 A1 20050203, 62 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-866180 20040614. PRIORITY: US 2003-2003/PV478403 20030613.

AB The present invention provides compds. of the formula X-R1-D-[Dpr, Orn or Lys](A)-R2 (Z)-D-[Dpr, Orn or Lys](B)-R3(Y)-NR4R5; or R1 (X)-D-[Dpr, Orn or Lys](A)-R2 (Z)-D-[Dpr, Orn or Lys](B)-R3(Y)-NR4R5, in which X is a hard acid cation chelator, a soft acid cation chelator or Ac-, R1, R2 and R3 are independently selected from a covalent bond or one or more D-amino acids that can be the same or different, Y is a hard acid cation chelator, a soft acid cation chelator or absent, Z is a hard acid cation chelator, a soft acid cation chelator or absent, and A and B are haptens or hard acid cation chelators and can be the same or different, and R4 and R5 are independently selected from the group consisting of hard acid cation chelators, soft acid cation chelators, enzymes, therapeutic agents, diagnostic agents and H. Multi-specific antibodies against a targetable construct are used that are capable of carrying one or more diagnostic or therapeutic agents. By using this approach the characteristics of the chelator, metal chelate complex, therapeutic agent or diagnostic agent can be varied to accommodate differing applications, without raising new multi-specific antibodies. The present invention also provides methods of using these compds. in radioimmunotherapy and radiol. diagnosis and kits containing the compds.

L11 ANSWER 3 OF 14 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

2005385776 EMBASE Therapeutic relevance of **targeting** nuclear factor kappaB with transcription factor decoy molecules. Gambari R.. R. Gambari, Department of Biochemistry and Molecular Biology, Section of Molecular Biology, Via Fossato di Mortara 74, 44100 Ferrrara, Italy. gam@unife.it. Drug Design Reviews Online Vol. 2, No. 5, pp. 397-407 2005.
Refs: 134.
ISSN: 1567-2697.
URL: http://saturn.bids.ac.uk/cgi-bin/ds_deliver/1/u/d/ISIS/20785657.1/ben/ddro/2005/00000002/00000005/art00006/BE02F56BE84F895A1124704830A9CEA75B80621FE5.pdf?link=http://www.ingentaconnect.com/error/delivery&format=pdf. Pub. Country: Netherlands. Language: English. Summary Language: English.

ED Entered STN: 20050929

AB Transcription factors belonging to the NF-kappaB superfamily are involved in several human pathologies, as well as in biological processes facilitating the onset of diseases. Among well established functions of NF-kappa B factors is the promotion of osteoclast differentiation in osteopenic diseases, the enhancement of inflammatory processes in cystic fibrosis, the involvement in asthma and pulmonary diseases associated to dust or smoke. In consideration of these roles of NF-kappaB, **targeting** of these transcription factors could be of great interest. A very promising approach to alter NF-kappaB regulated gene expression is the transcription factor decoy (TFD) strategy. The TFD approach employs double stranded oligodeoxyribonucleic acids mimicking the NF-kappaB binding sites or bioactive analogues; therefore, treatment of cells with these decoy molecules causes a binding of NF-kappaB factors to

them and not to the target promoter sequences, leading to a strong inhibition of NF-kappaB dependent biological functions. Decoy molecules **targeting** NF-kappaB factors were found in vitro inducers of apoptosis, and strong inhibitors of cell cycle progression, and TNF-alpha induced gene expression in several experimental cell systems. In vivo, decoy molecules **targeting** NF-kappaB factors were employed for prolonged survival of renal allografts, regression of atopic dermatitis, and cardiac protective effects. Therefore, the design and development of novel molecules able to target NF-kappaB, including modified oligonucleotides, LNA (locked nucleic acids) and peptide nucleic acids (PNA) based transcription factors decoys are of great interest. In this respect, TFD activity of double stranded PNA-DNA-PNA chimeras has been demonstrated to be useful to inhibit NF-kappaB dependent functions.

L11 ANSWER 4 OF 14 MEDLINE on STN DUPLICATE 1

2005092527. PubMed ID: 15721390. Lymphoid tissue **targeting** of anti-HIV drugs using **liposomes**. Desormeaux Andre; Bergeron Michel G. (Centre de Recherche en Infectiologie, Centre Hospitalier Universitaire de Quebec, Quebec, Canada.) Methods in enzymology, (2005) 391 330-51. Journal code: 0212271. ISSN: 0076-6879. Pub. country: United States. Language: English.

AB Considering that HIV-1 accumulates and replicates actively within lymphoid tissues, any strategy that will decrease viral stores in these tissues might be beneficial to the infected host. Follicular dendritic cells (FDC), B lymphocytes, antigen-presenting cells like macrophages, and activated CD4(+) T cells are abundant in lymphoid tissues, and all express substantial levels of the **HLA-DR** determinant of the major histocompatibility complex class II (MHC-II). Monocyte-derived macrophages, which are also CD4(+) and express **HLA-DR**, are considered to be the most frequent hosts of HIV-1 in tissues of infected individuals. This chapter describes a method for the generation of sterically stabilized immunoliposomes grafted with anti-**HLA-DR** antibodies that allows efficient delivery of drugs to lymphoid tissues. The method first involves the production of murine **HLA-DR** (clone Y-17, IgG(2b)) and human **HLA-DR** (clone 2.06, IgG(1)) antibodies from hybridomas in mice and their purification from ascites fluids. This step is followed by the production of Fab' fragments of antibodies 2.06 and Y-17 that are grafted at the surface of sterically stabilized immunoliposomes instead of the complete IgG to reduce their immunogenicity. The preparation of sterically stabilized **liposomes**, the composition of which allows an efficient entrapment and retention of several drugs, by the method of thin lipid film hydratation followed by extrusion through polycarbonate membranes is then described. This step is followed by the removal of unencapsulated drug, when present, by low-speed centrifugation of the liposomal preparation through a Sephadex G-50 column. These **liposomes** contain a fixed amount of poly(ethylene glycol) chain terminated by a maleimide reactive group for the coupling of Fab' fragments. The procedure for the coupling of Fab' fragments at the surface of sterically stabilized **liposomes** and the removal of uncoupled fragments of antibodies is described. In vitro binding studies of sterically stabilized immunoliposomes to cell lines expressing different surface levels of the mouse or human **HLA-DR** determinant of MHC-II demonstrate that these **liposomes** are very specific. When compared with conventional **liposomes**, the subcutaneous administration in the upper back, below the neck, of mice of anti-**HLA-DR** immunoliposomes resulted in a 2.9 and 1.6 times greater accumulation in the cervical and brachial lymph nodes, respectively. The use of sterically stabilized immunoliposomes increases 2 to 4.6 times the concentration of **liposomes** in all tissues, with a peak accumulation at 240 h in brachial, inguinal, and popliteal lymph nodes and at 360 h or greater in cervical lymph nodes. A single bolus injection of indinavir given subcutaneously to mice results in no significant drug levels in lymphoid organs. Most of the injected drug

accumulates in the liver and is totally cleared within 24 h postadministration. In contrast, sterically stabilized immunoliposomes are very efficient in delivering high concentrations of indinavir to lymphoid tissues for at least 15 days postinjection. The drug accumulation in all tissues leads to a 21- to 126-fold increased accumulation when compared with the free agent. Anti-**HLA-DR** immunoliposomes containing indinavir are as efficient as the free agent in inhibiting HIV-1 replication in PM1 cells that express high levels of cell surface **HLA-DR**. Sterically stabilized anti-**HLA-DR** immunoliposomes mostly accumulate in the cortex in which follicles (B cells and FDCs) are located, and in parafollicular areas in which T cells, interdigitating dendritic cells, and other accessory cells are abundant. The delivery of drugs in this area of the lymph nodes could represent a convenient strategy to inhibit more efficiently HIV-1 replication. Although the method described in this chapter is specific to the coupling of anti-**HLA-DR** antibodies, any antibody fragment or peptide specific for an antigen present in relatively large quantities at the surface of lymphoid cells, that is anchored to the surface of sterically stabilized **liposomes** with an appropriate coupling method, can be used to concentrate drugs within target tissues and improve the therapeutic effect of drugs.

L11 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

2003:719520 Document No. 139:259964 Bispecific antibody mutants with enhanced rate of clearance for diagnosis and treatment of immune, autoimmune, cardiovascular and neurological diseases. Qu, Zhengxing; Hansen, Hans; Goldenberg, David M. (Immunomedics, Inc., USA; McCall, John Douglas). PCT Int. Appl. WO 2003074569 A2 20030912, 68 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-GB871 20030303. PRIORITY: US 2002-2002/PV361037 20020301.

AB A mutant bispecific antibody that includes (a) a human hinge constant region from IgG having one or more amino acid mutations in the CH2 domain, (b) two scFvs; and (c) two Fvs has been constructed. This type of antibody displays enhanced clearance, which has been found to be particularly useful in the context of pre-**targeting** methods. The bispecific antibody mutants are useful for conjugated with therapeutic or diagnostic agents for diagnosis and treatment of immune disease, autoimmune disease, cardiovascular disease, neurol. disease, organ graft rejection, or graft vs. host disease.

L11 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

2003:836381 Document No. 139:341719 Use of bi-specific antibodies for pre-**targeting** diagnosis and therapy. Goldenberg, David M.; Hansen, Hans J.; Leung, Shui-on; McBride, William J.; Qu, Zhengxing (Immunomedics, Inc., USA). U.S. Pat. Appl. Publ. US 2003198595 A1 20031023, 59 pp., Cont.-in-part of U.S. Ser. No. 823,746. (English). CODEN: USXXCO. APPLICATION: US 2002-150654 20020517. PRIORITY: US 1998-PV90142 19980622; US 1998-PV104156 19981014; US 1999-382186 19990823; US 2001-2001/823746 20010403.

AB The present invention relates to a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable construct. The targetable construct comprises a carrier portion which comprises or bears at least one epitope recognizable by at least one arm of said bi-specific antibody or antibody fragment. The targetable construct further comprises one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the bi-specific antibodies or antibody fragments, as well as methods for using

them.

L11 ANSWER 7 OF 14 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2002034261 EMBASE Targeted delivery of indinavir to HIV-1 primary reservoirs with immunoliposomes. Gagne J.-F.; Desormeaux A.; Perron S.; Tremblay M.J.; Bergeron M.G.. M.G. Bergeron, Centre de Recherche en Infectiologie, Centre Hospitalier Univ. de Quebec, Universite Laval, 2705 Blvd Laurier, Quebec, Que., Canada. michel.g.bergeron@crchul.ulaval.ca. Biochimica et Biophysica Acta - Biomembranes Vol. 1558, No. 2, pp. 198-210 1 Feb 2002. Refs: 44.
ISSN: 0005-2736. CODEN: BBBMBS
S 0005-2736(01)00432-1. Pub. Country: Netherlands. Language: English. Summary Language: English.

ED Entered STN: 20020207

AB The tissue distribution of indinavir, free or incorporated into sterically stabilized anti-**HLA-DR** immunoliposomes, has been evaluated after a single subcutaneous injection to C3H mice. Administration of free indinavir resulted in low drug levels in lymphoid organs. In contrast, sterically stabilized anti-**HLA-DR** immunoliposomes were very efficient in delivering high concentrations of indinavir to lymphoid tissues for at least 15 days post-injection increasing by up to 126 times the drug accumulation in lymph nodes. The efficacy of free and immunoliposomal indinavir has been evaluated in vitro. Results showed that immunoliposomal indinavir was as efficient as the free agent to inhibit HIV-1 replication in cultured cells. The toxicity and immunogenicity of repeated administrations of liposomal formulations have also been investigated in rodents. No significant differences in the levels of hepatic enzymes of mice treated with free or liposomal indinavir were observed when compared to baseline and control untreated mice. Furthermore, histopathological studies revealed no significant damage to liver and spleen when compared to the control group. **Liposomes** bearing Fab' fragments were 2.3-fold less immunogenic than **liposomes** bearing the entire IgG. Incorporation of antiviral agents into sterically stabilized immunoliposomes could represent a novel therapeutic strategy to target specifically HIV reservoirs and treat more efficiently this retroviral infection.

L11 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

2000:790356 Document No. 133:340273 Methods and formulations for **targeting** infectious agents bearing host cell proteins. Bergeron, Michel G.; Desormeaux, Andre; Tremblay, Michel J. (Infectio Recherche Inc., Can.). PCT Int. Appl. WO 2000066173 A2 20001109, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-CA469 20000503. PRIORITY: CA 1999-2270600 19990503.

AB A formulation is disclosed for the treatment of diseases caused by an infectious agent which acquires host membranes protein during its life cycle. The formulation is a **targeting** pharmaceutical composition It comprises a ligand capable of binding the host membrane proteins coupled to a lipid-comprising vesicle, which may comprise or not a drug effective in the treatment of the disease. Specific **liposomes** bearing anti-**HLA-DR** or anti-CD4 antibodies comprising or not antiviral drugs, namely anti-HIV drugs, are disclosed and claimed. A method of formulation as well as a method of using the formulation in the treatment of a disease are also disclosed.

L11 ANSWER 9 OF 14 MEDLINE on STN DUPLICATE 3

2001338262. PubMed ID: 11101055. **Targeting** cell-free HIV and virally-infected cells with anti-**HLA-DR** immunoliposomes containing amphotericin B. Bestman-Smith J; Desormeaux A; Tremblay M J; Bergeron M G. (Centre de Recherche en Infectiologie, Centre Hospitalier Universitaire de Quebec, Canada.) AIDS (London, England), (2000 Nov 10) 14 (16) 2457-65. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To evaluate the ability of **liposomes** bearing anti-**HLA-DR** Fab' fragments (immunoliposomes) and containing amphotericin B (AmB) to target and neutralize cell-free HIV-1 particles and virally-infected cells. METHODS: The effect of AmB on the attachment and fusion of HIV-1(NL4-3) to Jurkat E6.1 cells has been evaluated using a p24 enzymatic assay. The ability of AmB to inhibit HIV-1-based luciferase reporter viruses pseudotyped with HXB2, AML-V and VSV-G envelopes has been evaluated in Jurkat E6.1 cells. The efficacy of free and immunoliposomal AmB to inhibit cell-free HIV, that have incorporated or not **HLA-DR** molecules, has been evaluated in **HLA-DR** /negative (NEG) 1G5 T cells and **HLA-DR**/positive (POS) Mono Mac 1 cells. RESULTS: AmB inhibited HIV infectivity independently of the nature of viral envelope proteins. Pretreatment of HIV with AmB had no major effect on viral attachment and fusion process to Jurkat E6.1 cells. Immunoliposomal AmB (0.5 microg/ml) led to a 77% inhibition of replication of **HLA-DR**/POS HIV-1 with no cell toxicity, whereas free AmB had no significant antiviral activity at this concentration. A complete inhibition of viral replication was observed following incubation of viruses with immunoliposomal AmB (2.5 microg/ml). Anti-**HLA-DR** immunoliposomes containing AmB had no effect on the infectivity of **HLA-DR**/NEG HIV-1 particles in **HLA-DR**/NEG T lymphoid cells but completely inhibited replication of viruses in an **HLA-DR** /POS monocytic cell line. CONCLUSION: The incorporation of neutralizing agents in anti-**HLA-DR** immunoliposomes could represent a novel therapeutic strategy to specifically target cell-free HIV particles and virally-infected cells to treat HIV infection more efficiently.

L11 ANSWER 10 OF 14 MEDLINE on STN DUPLICATE 4

2001048034. PubMed ID: 11018661. Sterically stabilized **liposomes** bearing anti-**HLA-DR** antibodies for **targeting** the primary cellular reservoirs of HIV-1. Bestman-Smith J; Gourde P; Desormeaux A; Tremblay M J; Bergeron M G. (Centre de Recherche en Infectiologie, Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, 2705 Blvd Laurier, G1V 4G2, Quebec, QC, Canada.) Biochimica et biophysica acta, (2000 Sep 29) 1468 (1-2) 161-74. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB The ability of **liposomes** bearing anti-**HLA-DR** Fab' fragments at the end termini of polyethyleneglycol chains (sterically stabilized immunoliposomes) to target **HLA-DR** expressing cells and increase the accumulation of **liposomes** into lymphoid organs has been evaluated and compared to that of conventional **liposomes**, sterically stabilized **liposomes** and conventional immunoliposomes after a single subcutaneous injection to mice. The accumulation of sterically stabilized **liposomes** in lymph nodes was higher than that of conventional **liposomes.** Sterically stabilized immunoliposomes accumulated much better than conventional immunoliposomes in all tissues indicating that the presence of PEG has an important effect on the uptake of immunoliposomes by the lymphatic system. Fluorescence microscopy studies showed that sterically stabilized **liposomes** are mainly localized in macrophage-rich areas such as the subcapsular region of lymph nodes and in the red pulp and marginal zone of the spleen. In contrast, sterically stabilized immunoliposomes mostly accumulated in the cortex in which follicles are located and in the white pulp of the spleen. As the human **HLA-DR** determinant of the major histocompatibility complex class II is expressed on activated CD4+ T lymphocytes and antigen presenting cells

such as monocyte/macrophages and dendritic cells, known as the cellular reservoirs of HIV-1, **liposomes** bearing anti-**HLA**-**DR** antibodies constitute an attractive approach to concentrate drugs in HIV-1 reservoirs and improve their therapeutic effect.

L11 ANSWER 11 OF 14 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

2000260421 EMBASE Controlled release of antiretroviral drugs. Von Briesen H.; Ramge P.; Kreuter J.. H. Von Briesen, Dept. of Pharmaceutical Research, J.N. Goethe University, Frankfurt, Germany. AIDS Reviews Vol. 2, No. 1, pp. 31-38 2000.
Refs: 36.
ISSN: 1139-6121. CODEN: ADRVF6
Pub. Country: Spain. Language: English. Summary Language: English.

ED Entered STN: 20000810

AB The treatment of AIDS using combinations of antiretroviral drugs has highly reduced the HIV-1 related morbidity and mortality, provided that the plasma viral load can be maintained as low as possible. However, eradication of the virus does not seem attainable with the present strategies of interventions which is due to two major obstacles: If resistant mutations appear the virus will escape further treatment, and latent virus reservoirs exist which cannot be reached with the current treatment regimens. One of these sanctuaries is the mononuclear phagocyte system (MPS) with its HIV-1 target cells, such as monocytes/macrophages (MO/MAC), dendritic cells (DC) and Langerhans cells which can be considered as primary cells for viral entry, and subsequently are responsible for distribution of the virus throughout the organism into various tissues. Colloidal drug carriers are easily phagocytosed by MO/MAK. Therefore, they can facilitate the uptake of antiviral drugs by these cells and may enable a considerably improved AIDS therapy. The present article summarises strategies which allow the **targeting** of antiviral drugs to these cells by the use of carrier systems including nanoparticles, **liposomes**, immunoliposomes or red blood cells.

L11 ANSWER 12 OF 14 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1999:198212 The Genuine Article (R) Number: 175QB. Presentation of antigens internalized through the B cell receptor requires newly synthesized MHC class II molecules. Forquet F (Reprint); Barois N; Machy P; Trucy J; Zimmermann V S; Leserman L; Davoust J. Ctr Immunol Marseille Luminy, Parc Sci Luminy, Case 906, F-13288 Marseille 9, France (Reprint); Ctr Immunol Marseille Luminy, Parc Sci Luminy, F-13288 Marseille 9, France. JOURNAL OF IMMUNOLOGY (15 MAR 1999) Vol. 162, No. 6, pp. 3408-3416. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Exogenous Ags taken up from the fluid phase ran he presented by both newly synthesized and recycling MHC class II molecules, However, the presentation of Ags internalized through the B cell receptor (BCR) has not been characterized with respect to whether the class II molecules with which they become associated are newly synthesized or recycling. We show that the presentation of Ag taken up by the BCR requires protein synthesis in splenic a cells and in B lymphoma cells. Using B tells transfected with full-length I-A(k) molecules or molecules truncated in cytoplasmic domains of their alpha- or beta-chains, we further show that when an Ag is internalized by the BCR, the cytoplasmic tails of class II molecules differentially control the presentation of antigenic peptides to specific T cells depending upon the importance of proteolytic processing in the production of that peptide, Integrity of the cytoplasmic tail of the I-A(k) beta-chain is required for the presentation of the hen egg lysozyme determinant (46-61) following BCR internalization, but that dependence is not seen for the (34-45) determinant derived from the same protein. The tail of the beta-chain is also of importance for the dissociation of invariant chain fragments from class II molecules, Our results demonstrate that Ags internalized through the BCR are targeted to compartments

containing newly synthesized class II molecules and that the tails of class II beta-chains control the loading of determinants produced after extensive Ag processing.

L11 ANSWER 13 OF 14 MEDLINE on STN DUPLICATE 5
2000001973. PubMed ID: 10518698. **Targeting** lymph nodes with **liposomes** bearing anti-**HLA-DR** Fab' fragments.
Dufresne I; Desormeaux A; Bestman-Smith J; Gourde P; Tremblay M J; Bergeron M G. (Centre de Recherche en Infectiologie, Universite Laval, Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, 2705 Blvd. Laurier, Quebec, QC, Canada.) Biochimica et biophysica acta, (1999 Oct 15) 1421 (2) 284-94. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.
AB The ability of **liposomes** bearing anti-**HLA-DR** Fab' fragments to target cells expressing the human **HLA-DR** determinant of the major histocompatibility complex class II (MHC-II) has been evaluated and compared to that of conventional **liposomes.** Anti-**HLA-DR** immunoliposomes did not bind to **HLA-DR**-negative cells. In contrast, a high level of binding was observed following incubation of immunoliposomes with cells bearing important levels of human **HLA-DR.** The accumulation of conventional and murine anti-**HLA-DR** immunoliposomes in different tissues has been investigated following a single subcutaneous injection given in the upper back of C3H mice. Anti-**HLA-DR** immunoliposomes resulted in a much better accumulation in the cervical and brachial lymph nodes when compared to conventional **liposomes.** The accumulation in the liver was similar for both liposomal preparations, whereas an approximately twofold decrease in accumulation was observed for immunoliposomes in the spleen. Given that **HLA-DR** surface marker is expressed on monocyte/macrophages and activated CD4+ T lymphocytes, the primary cellular reservoirs of the human immunodeficiency virus (HIV), the use of **liposomes** bearing surface-attached anti-**HLA-DR** could constitute a convenient strategy to more efficiently treat this debilitating retroviral disease. Moreover, the reported incorporation of high amounts of host-encoded **HLA-DR** proteins by HIV particles renders the use of **liposomes** bearing anti-**HLA-DR** antibodies even more attractive.

L11 ANSWER 14 OF 14 MEDLINE on STN
95256641. PubMed ID: 7738361. Inhibition of interferon-gamma-induced intercellular adhesion molecule-1 expression on human keratinocytes by phosphorothioate antisense oligodeoxynucleotides is the consequence of antisense-specific and antisense-non-specific effects. Hertl M; Neckers L M; Katz S I. (Dermatology Branch, National Cancer Institute, Bethesda, Maryland 20892, USA.) Journal of investigative dermatology, (1995 May) 104 (5) 813-8. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.
AB Expression of intercellular adhesion molecule-1 (ICAM-1) by keratinocytes is an important event in the pathogenesis of T-cell-mediated inflammatory skin diseases. To determine if ICAM-1 expression could be selectively modulated, two antisense phosphorothioate oligonucleotides (S-ODN) **targeting** the translation initiation and 3' untranslated regions of ICAM-1 mRNA were added as lipid complexes to cultures of keratinocytes. Interferon-gamma was added after 24 h to induce ICAM-1 expression, which was quantitated by flow cytometry after 48 h. The S-ODN **targeting** the translation initiation site did not inhibit ICAM-1 expression at 0.2-20.0 microM. In contrast, 0.2-1.0 microM of the S-ODN **targeting** a site in the 3' untranslated region abrogated ICAM-1 expression in up to 75% of the keratinocytes; this inhibition was reversible when complementary sense S-ODN was added. Phosphodiester ODN (PD-ODN) **targeting** the same sites did not inhibit ICAM-1 expression on keratinocytes, most likely as a consequence of rapid degradation. Inhibition of ICAM-1 by the antisense S-ODN was selective; expression of beta 2-microglobulin, alpha 3-integrin, and beta 1-integrin

remained largely unaffected and interferon-gamma-induced **HLA-DR** expression was inhibited to a much lesser extent than ICAM-1. Antisense-non-specific inhibition was also noted in that two scrambled S-ODN with an identical nucleotide (14 of 20 cytosines) composition inhibited ICAM-1 expression in up to 44% of the keratinocytes, whereas a degenerate S-ODN did not. The data demonstrate the complex effects exerted by antisense S-ODN in that ICAM-1 expression was inhibited via antisense-non-specific mechanisms probably due to the intrinsic properties of the S-ODN as well as via the anticipated sequence-specific mechanisms.

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=> s HLA-DR
L12      77904 HLA-DR

=> s l12 and infectious agent
L13        105 L12 AND INFECTIOUS AGENT

=> s l13 and targeting
L14          2 L13 AND TARGETING

=> dup remove l14
PROCESSING COMPLETED FOR L14
L15          2 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> d l15 1-2 cbib abs

L15  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2005 ACS on STN
2000:790356   Document No. 133:340273  Methods and formulations for
     targeting infectious agents bearing host cell
     proteins.  Bergeron, Michel G.; Desormeaux, Andre; Tremblay, Michel J.
     (Infectio Recherche Inc., Can.).  PCT Int. Appl. WO 2000066173 A2
     20001109, 45 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA,
     BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB,
     GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
     LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
     SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
     ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH,
     CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE,
     NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.  APPLICATION: WO
     2000-CA469 20000503.  PRIORITY: CA 1999-2270600 19990503.
AB   A formulation is disclosed for the treatment of diseases caused by an
     infectious agent which acquires host membranes protein
     during its life cycle.  The formulation is a targeting
     pharmaceutical composition  It comprises a ligand capable of binding the host
     membrane proteins coupled to a lipid-comprising vesicle, which may
     comprise or not a drug effective in the treatment of the disease.
     Specific liposomes bearing anti-HLA-DR or anti-CD4
     antibodies comprising or not antiviral drugs, namely anti-HIV drugs, are
     disclosed and claimed.  A method of formulation as well as a method of
     using the formulation in the treatment of a disease are also disclosed.

L15  ANSWER 2 OF 2  SCISEARCH  COPYRIGHT (c) 2005 The Thomson Corporation  on
     STN
1997:20054   The Genuine Article (R) Number: VZ128. In vivo functions mediated
     by the p41 isoform of the MHC class II-associated invariant chain.
     Takaesu N T (Reprint); Lower J A; Yelon D; Robertson E J; Bikoff E K.
     HARVARD UNIV, DEPT MOL & CELLULAR BIOL, BIOL LABS, CAMBRIDGE, MA 02138.
     JOURNAL OF IMMUNOLOGY (1 JAN 1997) Vol. 158, No. 1, pp. 187-199. ISSN:
     0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE,
     BETHESDA, MD 20814. Language: English.
     *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB        We used a ''hit and run'' gene targeting strategy to
     generate mice expressing only the p41 isoform of the conserved invariant
     (Ii) chain associated with MHC class II molecules, In contrast to mutants
     expressing only p31 Ii chain, a small proportion of A alpha(b)A beta(b)
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molecules produced by these animals have reduced mobilities in SDS-PACE and appear incompletely processed, Nonetheless, class II surface expression, peptide occupancy, CD4(+) T cell maturation, and proliferative responses toward intact protein Ags are efficiently reconstituted, Moreover, spleen cells exclusively expressing p41 or p31 alone display equivalent dose-response curves in Ag presentation assays, Similar conclusions were reached analyzing mutants expressing two independent MHC haplotypes, Overall, these results demonstrate that Ii chain functional activities as a class II-specific chaperone are largely shared by p31 and p41 isoforms in the intact animal, Mutant mouse strains producing only p31 or p41 under control of endogenous regulatory elements responsible for constitutive and inducible Ii chain expression should prove useful for dissecting the contributions of these isoforms to diverse CD4(+) T cell responses in vivo, such as those responsible for Ab production, inflammatory responses, autoimmune diseases, and protection against **infectious agents.**

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=> dup remove l14
PROCESSING COMPLETED FOR L14
L16            2 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> dup remove l13
PROCESSING COMPLETED FOR L13
L17           59 DUP REMOVE L13 (46 DUPLICATES REMOVED)

=> s l17 and liposome
L18            3 L17 AND LIPOSOME

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19            3 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l19 1-3 cbib abs

L19  ANSWER 1 OF 3  SCISEARCH  COPYRIGHT (c) 2005 The Thomson Corporation  on
     STN
2001:443882   The Genuine Article (R) Number: 437BP. Peptide vaccines and
     peptide libraries.  Wiesmuller K H (Reprint); Fleckenstein B; Jung G. EMC
     Microcollect GmbH, Sindelfinger Str 3, D-72070 Tubingen, Germany
     (Reprint); EMC Microcollect GmbH, D-72070 Tubingen, Germany; Univ
     Tubingen, Inst Organ Chem, D-72076 Tubingen, Germany. BIOLOGICAL CHEMISTRY
      (APR 2001) Vol. 382, No. 4, pp. 571-579. ISSN: 1431-6730. Publisher:
     WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY.
     Language: English.
     *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB        Synthetic immunogens, containing built-in adjuvanticity, B cell, T
     helper cell and CTL epitopes or mimotopes, are ideal and invaluable tools
     to study the immune response with respect to antigen processing and
     presentation.  This serves as a basis for the development of complete and
     minimal vaccines which do not need large carrier proteins, further
     adjuvants, liposome formulations or other delivery systems.
          Combinatorial peptide libraries, either completely random or
     characterized by one or several defined positions, are useful tools for
     the identification of the critical features of B cell epitopes and of MHC
     class I and class II binding natural and synthetic epitopes.  The complete
     activity pattern of an O/X-n library with hundreds of peptide collections,
     each made up from billions of different peptides, represents the ranking
     of amino acid residues mediating contact to the target proteins of the
     immune system.  Combinatorial libraries support the design of peptides
     applicable in vaccination against infectious agents as
     well as therapeutic tumour vaccines.
          Using the principle of lipopeptide vaccines, strong humoral and
     cellular immune responses could be elicited.  The lipopeptide vaccines are
     heat-stable, non-toxic, fully biodegradable and can be prepared on the
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basis of minimized epitopes by modern methods of multiple peptide synthesis. The lipopeptides activate the antigen-presenting macrophages and B cells and have been recently shown to stimulate innate immunity by specific interaction with receptors of the Toll family.

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
2000:790356 Document No. 133:340273 Methods and formulations for targeting **infectious agents** bearing host cell proteins. Bergeron, Michel G.; Desormeaux, Andre; Tremblay, Michel J. (Infectio Recherche Inc., Can.). PCT Int. Appl. WO 2000066173 A2 20001109, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-CA469 20000503. PRIORITY: CA 1999-2270600 19990503.

AB A formulation is disclosed for the treatment of diseases caused by an **infectious agent** which acquires host membranes protein during its life cycle. The formulation is a targeting pharmaceutical composition It comprises a ligand capable of binding the host membrane proteins coupled to a lipid-comprising vesicle, which may comprise or not a drug effective in the treatment of the disease. Specific **liposomes** bearing anti-**HLA-DR** or anti-CD4 antibodies comprising or not antiviral drugs, namely anti-HIV drugs, are disclosed and claimed. A method of formulation as well as a method of using the formulation in the treatment of a disease are also disclosed.

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
1998:424096 Document No. 129:94451 Superantigen based methods and compositions for treatment of diseases. Terman, David S. (Terman, David S., USA). PCT Int. Appl. WO 9826747 A2 19980625, 140 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US23637 19971217. PRIORITY: US 1996-33172 19961217; US 1997-44074 19970417.

AB The present invention relates to therapeutic methods and compns. employing superantigens. Methods and compns. employing superantigens and immunotherapeutic proteins in combination with one another have been found to provide more effective treatment than either component used alone. Superantigens, in conjunction with one or more addnl. immunotherapeutic antigens, may be used to either induce a therapeutic immune response directed against a target or to inhibit a disease causing immune response. Specific combinations of superantigens and immunotherapeutic antigens are used to treat specific diseases. The induction (or augmentation) of a desired immune against a target may be used, for example, to kill cancer cells or kill the cells or an **infectious agent.** The inhibition of an immune response, e.g., through the induction of T cell anergy, may be used to reduce the symptoms of an autoimmune disease. Diseases that may be treated by the methods and compns. of the invention include neoplastic diseases, infectious diseases, and autoimmune diseases. One aspect of the invention is to provide methods for the treatment of diseases comprising the steps of administering an effective amount of a superantigen and an immunotherapeutic so as to have the desired therapeutic effect. The superantigen and immunotherapeutic antigen may be administered together as a mixture Alternatively, the superantigen and immunotherapeutic antigen may be administered sep. In one embodiment of the invention, the superantigen and immunotherapeutic antigen are administered to the patient in the form of a immunotherapeutic antigen-superantigen polymer of the invention. Another aspect of the invention is to provide methods for the treatment of diseases comprising the steps of incubating a lymphocyte population ex vivo a superantigen and an immunotherapeutic protein so as to either activate or anergize T cells

within the selected population.

=> d l17 1-59 cbib abs

L17 ANSWER 1 OF 59 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
2005401981 EMBASE Broadly targeted human cytomegalovirus-specific CD4(+) and CD8(+) T cells dominate the memory compartments of exposed subjects. Sylwester A.W.; Mitchell B.L.; Edgar J.B.; Taormina C.; Pelte C.; Ruchti F.; Sleath P.R.; Grabstein K.H.; Hosken N.A.; Kern F.; Nelson J.A.; Picker L.J.. L.J. Picker, Vaccine and Gene Therapy Institute, Departments of Pathology and Molecular Microbiology and Immunology, Oregon Health and Science University, Beaverton, OR 97006, United States. pickerl@ohsu.edu. Journal of Experimental Medicine Vol. 202, No. 5, pp. 673-685 5 Sep 2005.
Refs: 44.
ISSN: 0022-1007. CODEN: JEMEAV
URL: http://www.jem.org/cgi/reprint/202/5/673. Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20051013
AB Human cytomegalovirus (HCMV) infections of immunocompetent hosts are characterized by a dynamic, life-long interaction in which host immune responses, particularly of T cells, restrain viral replication and prevent disease but do not eliminate the virus or preclude transmission. Because HCMV is among the largest and most complex of known viruses, the T cell resources committed to maintaining this balance have never been characterized completely. Here, using cytokine flow cytometry and 13,687 overlapping 15mer peptides comprising 213 HCMV open reading frames (ORFs), we found that 151 HCMV ORFs were immunogenic for CD4(+) and/or CD8(+) T cells, and that ORF immunogenicity was influenced only modestly by ORF expression kinetics and function. We further documented that total HCMV-specific T cell responses in seropositive subjects were enormous, comprising on average .apprx.10% of both the CD4(+) and CD8(+) memory compartments in blood, whereas cross-reactive recognition of HCMV proteins in seronegative individuals was limited to CD8(+) T cells and was rare. These data provide the first glimpse of the total human T cell response to a complex **infectious agent** and will provide insight into the rules governing immunodominance and cross-reactivity in complex viral infections of humans. JEM .COPYRGT. The Rockefeller University Press.

L17 ANSWER 2 OF 59 MEDLINE on STN
2005025920. PubMed ID: 15653997. Anemia, allogenic blood transfusion, and immunomodulation in the critically ill. Raghavan Murugan; Marik Paul E. (Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.) Chest, (2005 Jan) 127 (1) 295-307. Ref: 152. Journal code: 0231335. ISSN: 0012-3692. Pub. country: United States. Language: English.
AB Anemia and allogenic RBC transfusions are exceedingly common among critically ill patients. Multiple pathologic mechanisms contribute to the genesis of anemia in these patients. Emerging risks associated with allogenic RBC transfusions including the transmission of newer **infectious agents** and immune modulation predisposing the patient to infections requires reevaluation of current transfusion strategies. Recent data have suggested that a restrictive transfusion practice is associated with reduced morbidity and mortality during critical illness, with the possible exception of acute coronary syndromes. In this article, we review the immune-modulatory role of allogenic RBC transfusions in critically ill patients.

L17 ANSWER 3 OF 59 MEDLINE on STN
2004460703. PubMed ID: 15370569. Presence of dendritic cells, T lymphocytes, macrophages, B lymphocytes and glandular tissue in the human fetal larynx. Dietrich C; Jecker P; Tschernig T; Mann W J. (Department of

Otolaryngology, Mainz Medical School, Mainz, Germany.) Acta oto-laryngologica, (2004 Sep) 124 (7) 833-8. Journal code: 0370354. ISSN: 0001-6489. Pub. country: Norway. Language: English.

AB OBJECTIVE: The laryngeal mucosa starts to be exposed to **infectious agents** immediately after birth. The course of laryngeal infections in young children differs significantly from that in adults. The first line of defense encountered by an inhaled **infectious agent** is the mucosa-associated immune system, which includes immunocompetent cells and secretory components. The cellular elements are partially organized in a typical morphological pattern known as mucosa-associated lymphoid tissue (MALT). Differences in the ability of young children and adults to react to a laryngeal infection raise the questions of whether and to what extent immunocompetent cells are already present in the larynx at birth. These questions were investigated in this study. MATERIAL AND METHODS: Dendritic cells, T lymphocytes, B lymphocytes, macrophages and glands were examined and detected in an (immuno-)histological study of 8 fetal larynges (14th-22nd week of gestation). RESULTS: Immunocompetent cells and glands were present mainly in the epi- and subglottic regions and ventricular folds, whereas the glottis was largely spared. The pattern of distribution was scattered and no organized MALT was seen. CONCLUSION: Essential cell populations of a mucosa-associated immune system for the initiation of an immune response may exist in the human larynx at birth.

L17 ANSWER 4 OF 59 MEDLINE on STN DUPLICATE 1

2004273699. PubMed ID: 15172451. MHC class II tetramers containing influenza hemagglutinin and EBV EBNA1 epitopes detect reliably specific CD4(+) T cells in healthy volunteers. Ye Ming; Kasey Suha; Khurana Sumit; Nguyen Nga T; Schubert Scott; Nugent C Thomas; Kuus-Reichel Kristine; Hampl Johannes. (Cell Analysis Development Center, Beckman Coulter, Inc, San Diego, CA 92121, USA.) Human immunology, (2004 May) 65 (5) 507-13. Journal code: 8010936. ISSN: 0198-8859. Pub. country: United States. Language: English.

AB Tracking antigen specific T cells with major histocompatibility complex (MHC) tetramers has provided us with insights into the dynamics of the adaptive immune system and holds great promise to aid in patient management and drug and vaccine development. Progress has been made primarily using MHC class I tetramers to monitor CD8(+) T cells, whereas corresponding efforts to stain CD4(+) T cells with class II tetramers have not been as successful. Two major reasons have been proposed for this lack of progress: (1). The frequency of antigen-specific CD4(+) T cells is lower than the frequency of CD8(+) T cells and (2). some, but not all, antigen- specific CD4(+) T cells can bind tetramer because of low functional avidity. In this study, we asked if CD4(+) T cells specific for common human viruses (e.g., influenza and Epstein-Barr) can be detected in healthy individuals previously exposed to them. We were able to clearly detect specific CD4(+) T cells in all donors after in vitro expansion of peripheral blood mononuclear cells. Furthermore, we observe a clear separation of tetramer negative and tetramer positive CD4(+) T cells in most samples similar to patterns commonly seen with class I tetramers. The data indicate that MHC class II tetramers can be used reliably for the identification of CD4(+) T cells specific for ubiquitous **infectious agents** in normal donors.

L17 ANSWER 5 OF 59 EMBASE on STN

2004172233 EMBASE Are Polymyalgia Rheumatica and Giant Cell Arteritis the Same Disease?. Cantini F.; Niccoli L.; Storri L.; Nannini C.; Olivieri I.; Padula A.; Boiardi L.; Salvarani C.. Dr. F. Cantini, 2nd Divisione di Medicina, Unita Reumatologica, Osp. Misericordia e Dolce di Prato, Piazza Ospedale, 1, 59100 Prato, Italy. fcantini@conmet.it. Seminars in Arthritis and Rheumatism Vol. 33, No. 5, pp. 294-301 2004.
Refs: 87.
ISSN: 0049-0172. CODEN: SAHRBF
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 20040513
AB Objective: To summarize the evidence about the relationship between polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). Methods: Review of relevant articles from the English-language literature. Results: Epidemiologic studies suggest that PMR and GCA are closely related conditions affecting people over 50 years and frequently occurring in the same patient. PMR symptoms have been observed in 40 to 60 percent of GCA clinical series. Also, temporal artery biopsy may yield positive results for GCA in patients with isolated PMR. Conflicting HLA-DRB1 genotype results have been reported, and recent studies have shown that PMR and GCA have different expression of RANTES, TNFα microsatellite, and IL-6 promoter genetic polymorphisms. Search for a possible common **infectious agent** have yielded disappointing results. Although parvovirus B19 DNA is present in the artery wall of patients with GCA, this virus may be only an innocent bystander. Cytokine studies on a limited number of temporal artery biopsy specimens have shown that interferon-γ is produced in GCA and not in PMR, suggesting that this cytokine may be crucial to the development of overt vasculitis. Conclusions: PMR and GCA frequently occur together but no definitive conclusions can be drawn about the nature of this association.

L17 ANSWER 6 OF 59 MEDLINE on STN DUPLICATE 2
2004048148. PubMed ID: 14750076. Acute graft-versus-host disease and steroid treatment impair CD11c+ and CD123+ dendritic cell reconstitution after allogeneic peripheral blood stem cell transplantation. Arpinati Mario; Chirumbolo Gabriella; Urbini Benedetta; Bonifazi Francesca; Bandini Giuseppe; Sauntharajah Yogen; Zagnoli Alessandra; Stanzani Marta; Falcioni Sadia; Perrone Giulia; Tura Sante; Baccarani Michele; Rondelli Damiano. (Research Center for Transplant Immunology, Institute of Hematology and Medical Oncology Seragnoli, University of Bologna, Italy.. arpinati@med.unibo.it) . Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, (2004 Feb) 10 (2) 106-15. Journal code: 9600628. ISSN: 1083-8791. Pub. country: United States. Language: English.
AB Human dendritic cells (DC) comprise 2 subsets-plasmacytoid CD123(+) and myeloid CD11c(+) DC-that may have distinct roles in the regulation of immunity after allogeneic hematopoietic stem cell transplantation. In this study, we analyzed the kinetics of CD123(+) DC and CD11c(+) DC reconstitution in 31 patients who underwent transplantation with allogeneic granulocyte colony-stimulating factor-mobilized peripheral blood (PB) stem cells from HLA-identical sibling donors after myeloablative conditioning. Lineage marker-negative **HLA-DR**(+) CD11c(+) CD11c(+) DC and lineage marker-negative **HLA-DR**(+) CD123(+) CD123(+) DC, as well as monocytes and lymphoid subsets, were enumerated in donor grafts and in the PB of patients at various time points after transplantation. Reconstitution of both CD11c(+) DC and CD123(+) DC to normal levels occurred within 6 to 12 months and was not affected by the diagnosis, preparatory regimen, or graft composition. However, PB CD11c(+) DC and CD123(+) DC counts were significantly reduced in patients with acute GVHD grade II to IV (at 1 and 3 months) and grade I (at 1 month). Patients with chronic GVHD instead showed reduced CD123(+) DC counts only 6 months after transplantation. Moreover, treatment with steroids (>0.1 mg/kg) was significantly associated with reduced PB CD11c(+) DC and CD123(+) DC counts at all time points after transplantation. In multivariate analysis, only acute GVHD affected DC reconstitution early after transplantation. These results will prompt new studies addressing whether DC reconstitution correlates with immunity against **infectious agents** or with graft-versus-tumor reactions after PB stem cell allotransplantation.

L17 ANSWER 7 OF 59 MEDLINE on STN DUPLICATE 3
2004594013. PubMed ID: 15567090. Antigenic complementarity among AIDS-associated **infectious agents** and molecular mimicry of lymphocyte proteins as inducers of lymphocytotoxic antibodies

and circulating immune complexes. Root-Bernstein Robert S. (Department of Physiology, Michigan State University, 2174 Biomedical and Physical Sciences Building, East Lansing, MI 48824, USA.. rootbern@msu.edu) . Journal of clinical virology : official publication of the Pan American Society for Clinical Virology, (2004 Dec) 31 Suppl 1 S16-25. Journal code: 9815671. ISSN: 1386-6532. Pub. country: Netherlands. Language: English.

AB BACKGROUND: People at risk for acquired immunodeficiency syndrome (AIDS) have high rates of cofactor infections in addition to HIV, including cytomegalovirus, hepatitis viruses, Mycobacteria, Mycoplasmas, and Staphylococcus aureus. Most people with AIDS also develop lymphocytotoxic antibodies (LCTA) and circulating immune complexes (CIC). While HIV proteins mimic HLA antigens, many cofactor agents mimic CD4 antigens. It has therefore been proposed that cofactor infections may interact with HIV by producing complementary antigens that induce LCTA and CIC, and that the resulting immunological dysfunction is part of AIDS pathogenesis. OBJECTIVES: To test (1) whether HIV and its cofactor infections elicit complementary (idiotype-anti-idiotype) antibodies, and (2) if any of these antibodies mimic anti-lymphocyte antibodies. STUDY DESIGN: Two immunological methods are employed to test for antibody complementarity: (1) double antibody diffusion, a modification of Ouchterlony immunodiffusion, in which antibodies are tested for their ability to precipitate each other; (2) double-antibody ELISA, in which an antibody against one **infectious agent** is adsorbed to an ELISA plate and an antibody against a second agent is used to detect the first. RESULTS: Data on over a thousand double antibody diffusion (DAD) and about 70 DA-ELISA experiments are reported. These show that only specific pairs of antibodies are complementary: HIV-CMV; HIV-HBV; HIV-tuberculosis; HIV-mycoplasmas; HIV-S. aureus; and CMV-mycoplasmas. In addition, HIV antibodies precipitate CD4 antibodies; CMV antibodies precipitate **HLA-DR** antibodies; while mycobacteria and mycoplasma antibodies precipitate macrophage antibodies. CONCLUSIONS: Antibodies elicited by HIV infection can interact with antibodies elicited by cofactor infections to form CIC, and some of these antibodies mimic lymphocyte antibodies so that they may function as LCTA. Since LCTA and CIC are associated with increased lymphocyte death in AIDS, the immune response against cofactors in HIV may play a significant role in AIDS pathogenesis. The fact that both HIV and cofactors elicit antibodies with LCTA characteristics may pose problems for vaccine development.

L17 ANSWER 8 OF 59 EMBASE

2004517647 EMBASE Antigenic complementarity among AIDS-associated **infectious agents** and molecular mimicry of lymphocyte proteins as inducers of lymphocytotoxic antibodies and circulating immune complexes. Root-Bernstein R.S.. rootbern@msu.edu. Journal of Clinical Virology Vol. 31, No. SUPPL. 1, pp. S16-S25 2004.
Refs: 77.
ISSN: 1386-6532. CODEN: JCVIFB
S 1386-6532(04)00230-6. Pub. Country: Netherlands. Language: English. Summary Language: English.

ED Entered STN: 20041217

AB People at risk for acquired immunodeficiency syndrome (AIDS) have high rates of cofactor infections in addition to HIV, including cytomegalovirus, hepatitis viruses, Mycobacteria, Mycoplasmas, and Staphylococcus aureus. Most people with AIDS also develop lymphocytotoxic antibodies (LCTA) and circulating immune complexes (CIC). While HIV proteins mimic HLA antigens, many cofactor agents mimic CD4 antigens. It has therefore been proposed that cofactor infections may interact with HIV by producing complementary antigens that induce LCTA and CIC, and that the resulting immunological dysfunction is part of AIDS pathogenesis. To test (1) whether HIV and its cofactor infections elicit complementary (idiotype-anti-idiotype) antibodies, and (2) if any of these antibodies mimic anti-lymphocyte antibodies. Two immunological methods are employed to test for antibody complementarity: (1) double antibody diffusion, a

modification of Ouchterlony immunodiffusion, in which antibodies are tested for their ability to precipitate each other; (2) double-antibody ELISA, in which an antibody against one **infectious agent** is adsorbed to an ELISA plate and an antibody against a second agent is used to detect the first. Data on over a thousand double antibody diffusion (DAD) and about 70 DA-ELISA experiments are reported. These show that only specific pairs of antibodies are complementary: HIV-CMV; HIV-HBV; HIV-tuberculosis; HIV-mycoplasmas; HIV-S. aureus; and CMV-mycoplasmas. In addition, HIV antibodies precipitate CD4 antibodies; CMV antibodies precipitate **HLA-DR** antibodies; while mycobacteria and mycoplasma antibodies precipitate macrophage antibodies. Antibodies elicited by HIV infection can interact with antibodies elicited by cofactor infections to form CIC, and some of these antibodies mimic lymphocyte antibodies so that they may function as LCTA. Since LCTA and CIC are associated with increased lymphocyte death in AIDS, the immune response against cofactors in HIV may play a significant role in AIDS pathogenesis. The fact that both HIV and cofactors elicit antibodies with LCTA characteristics may pose problems for vaccine development.

L17 ANSWER 9 OF 59 EMBASE
2002460489 EMBASE [Autoimmune thyroiditis - An infectional disease?]. AUTOIMMUN THYROIDITIS - EN INFEKTIONSSYGDOM?. Rasmussen A.K.; Feldt-Rasmussen U.F.. A.K. Rasmussen, Medicinsk Endokrinologisk Klinik PE, H:S Rigshospitalet, DK-2100 Kobenhavn O, Denmark. Ugeskrift for Laeger Vol. 164, No. 50, pp. 5911-5915 9 Dec 2002.
Refs: 33.
ISSN: 0041-5782. CODEN: UGLAAD
Pub. Country: Denmark. Language: Danish. Summary Language: English; Danish.
ED Entered STN: 20030109
AB The aim was to review existing evidence of a possible role of **infectious agents** in the pathogenesis of autoimmune thyroid disease. Autoimmune thyroid disease is a polygenic, multifactorial disease in which genetically susceptible individuals are exposed to an environmental insult resulting in immune system activation. Different viruses (influenza B, rubella, retrovirus) have been associated with thyroiditis, but no single agent appears to be causative. There is no firm evidence of infection being an important trigger of autoimmune thyroid disease, and it has not been possible to isolate a microorganism neither by culture nor by molecular identification. Infection may be a precipitating factor in the development of autoimmune thyroid disease.

L17 ANSWER 10 OF 59 MEDLINE on STN DUPLICATE 4
2002405084. PubMed ID: 12075003. Genetic susceptibility to childhood common acute lymphoblastic leukaemia is associated with polymorphic peptide-binding pocket profiles in HLA-DPB1*0201. Taylor G Malcolm; Dearden Simon; Ravetto Paul; Ayres Michelle; Watson Pamela; Hussain Adiba; Greaves Mel; Alexander Freda; Eden Osborn B. (Immunogenetics Laboratory, St Mary's Hospital, Manchester M13 0JH, UK. (UKCCS Investigators. United Kingdom Childhood Cancer Study). gmtaylor@man.ac.uk) . Human molecular genetics, (2002 Jul 1) 11 (14) 1585-97. Journal code: 9208958. ISSN: 0964-6906. Pub. country: England: United Kingdom. Language: English.
AB In a previous study, we obtained preliminary evidence in a small series of patients (n = 63) suggesting that susceptibility to childhood common acute lymphoblastic leukaemia (c-ALL) was associated with an allele at the HLA-DPB1 locus, DPB1*0201. We have now tested this hypothesis by comparing the frequency of children with leukaemia (n = 982) who typed for specific DPB1 alleles and two groups of non-leukaemic children, one consisting of children with solid tumours, excluding lymphomas (n = 409), the other consisting of normal infants (n = 864). We found that significantly more children with c-ALL and T-ALL, but not pro-B ALL or acute non-ALL typed for DPB1*0201 as compared with children with solid tumours [odds ratio (OR), 95% confidence interval (CI) for c-ALL: 1.76,

1.20-2.56; T-ALL: 1.93, 1.01-3.80] and normal infants (OR, 95% CI for c-ALL: 1.83, 1.34-2.48; T-ALL: 2.00, 1.10-3.82). In childhood c-ALL, significantly more children than those with solid tumours or normal infants typed for DPB1 alleles coding specific polymorphic amino acids lining the antigen-binding site of the DPbeta1*0201 allotypic protein, suggesting that susceptibility to childhood c-ALL may be influenced by DPbeta ABS amino acid polymorphisms shared by DPbeta1*0201 and other DPbeta1 allotypes. These results point to a mechanism of c-ALL susceptibility that involves the presentation of specific antigenic peptides, possibly derived from **infectious agents**, by DPbeta1*0201-related allotypic proteins, leading to the activation of helper T cells mediating proliferative stress on preleukaemic cells.

L17 ANSWER 11 OF 59 MEDLINE on STN
2002164107. PubMed ID: 11895927. Direct costimulation of tumor-reactive CTL by helper T cells potentiate their proliferation, survival, and effector function. Giuntoli Robert L 2nd; Lu Jun; Kobayashi Hiroya; Kennedy Richard; Celis Esteban. (Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota 55905, USA.) Clinical cancer research : an official journal of the American Association for Cancer Research, (2002 Mar) 8 (3) 922-31. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

AB The survival and proliferation of CTL during the effector phase of the immune response is critical for the elimination of **infectious agents** and tumor cells. We report here that in an in vitro model system, the expansion and cytolytic function of tumor-reactive human CTL can be enhanced by CD4(+) helper T lymphocytes through costimulatory signals that are mediated by cell surface molecules. The results presented here suggest that costimulatory receptors on CTL such as CD27, CD134 (4-1BB), and MHC class II are capable of directly interacting with the corresponding ligands on T-helper lymphocytes resulting in enhanced proliferation and survival of the CTL during the effector phase of antitumor immune responses. These findings underline the importance of antigen-specific helper T lymphocytes for the regulation and maintenance of CTL immunity, and have implications for the design of therapeutic vaccines for cancer.

L17 ANSWER 12 OF 59 MEDLINE on STN DUPLICATE 5
2002358169. PubMed ID: 12089692. Analysis of human leukocyte antigens in patients with internal derangement of the temporomandibular joint. Henry Charles H; Nikaein Afzal; Wolford Larry M. (Baylor University Medical Center Transplantation Laboratory, Dallas, TX, USA.. chenry@pol.net) . Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons, (2002 Jul) 60 (7) 778-83. Journal code: 8206428. ISSN: 0278-2391. Pub. country: United States. Language: English.

AB PURPOSE: Spondyloarthropathy includes the subcategory of reactive arthritis (ReA). Spondyloarthropathies are commonly associated with certain human leukocyte antigen (HLA) alleles. Because we identified bacteria associated with ReA within the temporomandibular joint (TMJ), we now evaluate the frequency of HLA alleles in patients with TMJ pathology. PATIENTS AND METHODS: HLA typing of 129 patients (121 females and 8 males) performed by standard microcytotoxicity technique. Thirty patients had only class I (HLA-A and -B loci) evaluated. Ninety-nine patients had both class I and class II (**HLA-DR** loci) evaluated.
Identification of alleles at the C locus was not performed. The antigenic frequency in the study group was compared to US white control subjects using a 2-tailed Fisher's exact test with a Bonferroni multiple comparison adjustment. RESULTS: The following class I HLA alleles, -A1 (32%), -A2 (50%), -A3 (33%), -B7 (23%), -B14 (14%), -B35 (20%), and -B44 (36%), including the B7 cross-reactive group (CREG) (49%) and class II alleles -DR1 (25%) and -DR4 (34%), were found to have an increased frequency in our patient group. CONCLUSIONS: Our study shows an increased frequency of several alleles that have been previously associated with arthropathy, and the alleles of the B7 CREG, in patients with TMJ pathology. Patients with

these alleles may have an increased risk for the development of internal derangement of the TMJ as a consequence of the bacterial/ **infectious agents** and host interactions with the subsequent cytokine/inflammatory response being influenced by their HLA phenotype.

L17 ANSWER 13 OF 59 EMBASE
2002133982 EMBASE Genetic dissection of immunity to mycobacteria: The human model. Casanova J.-L.; Abel L.. J.-L. Casanova, Lab. of Human Genet. of Infect. Dis., Univ. Rene Descartes-INSERM U550, Necker Medical School, 156 rue de Vaugirard, 75015 Paris, France. casanova@necker.fr. Annual Review of Immunology Vol. 20, pp. 581-620 2002.
Refs: 209.
ISSN: 0732-0582. CODEN: ARIMDU
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20020502
AB Humans are exposed to a variety of environmental mycobacteria (EM), and most children are inoculated with live Bacille Calmette-Guerin (BCG) vaccine. In addition, most of the world's population is occasionally exposed to human-borne mycobacterial species, which are less abundant but more virulent. Although rarely pathogenic, mildly virulent mycobacteria, including BCG and most EM, may cause a variety of clinical diseases. Mycobacterium tuberculosis, M. leprae, and EM M. ulcerans are more virulent, causing tuberculosis, leprosy, and Buruli ulcer, respectively. Remarkably, only a minority of individuals develop clinical disease, even if infected with virulent mycobacteria. The interindividual variability of clinical outcome is thought to result in part from variability in the human genes that control host defense. In this well-defined microbiological and clinical context, the principles of mouse immunology and the methods of human genetics can be combined to facilitate the genetic dissection of immunity to mycobacteria. The natural infections are unique to the human model, not being found in any of the animal models of experimental infection. We review current genetic knowledge concerning the simple and complex inheritance of predisposition to mycobacterial diseases in humans. Rare patients with Mendelian disorders have been found to be vulnerable to BCG, a few EM, and M. tuberculosis. Most cases of presumed Mendelian susceptibility to these and other mycobacterial species remain unexplained. In the general population leprosy and tuberculosis have been shown to be associated with certain human genetic polymorphisms and linked to certain chromosomal regions. The causal vulnerability genes themselves have yet to be identified and their pathogenic alleles immunologically validated. The studies carried out to date have been fruitful, initiating the genetic dissection of protective immunity against a variety of mycobacterial species in natural conditions of infection. The human model has potential uses beyond the study of mycobacterial infections and may well become a model of choice for the investigation of immunity to **infectious agents.**

L17 ANSWER 14 OF 59 MEDLINE on STN DUPLICATE 6
2002045015. PubMed ID: 11756175. Human T-cell leukemia virus type 2 induces survival and proliferation of CD34(+) TF-1 cells through activation of STAT1 and STAT5 by secretion of interferon-gamma and granulocyte macrophage-colony-stimulating factor. Bovolenta Chiara; Pilotti Elisabetta; Mauri Massimiliano; Turci Marco; Ciancianaini Paolo; Fisicaro Paola; Bertazzoni Umberto; Poli Guido; Casoli Claudio. (AIDS Immunopathogenesis Unit, San Raffaele Scientific Institute, Milan, Italy.. c.bovolenta@hsr.it) . Blood, (2002 Jan 1) 99 (1) 224-31. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.
AB Human T-cell leukemia-lymphoma virus (HTLV) type-2 can induce the survival and proliferation of CD34(+) TF-1 cells deprived of interleukin (IL)-3. This effect did not require productive infection and occurred when HTLV-2 was produced from T cells (CMo), but not from B cells (BMo), unless the latter virus was complexed with anti-**HLA-DR** monoclonal

antibodies (mAbs). Cellular and molecular mechanisms triggered by HTLV-2 interaction with TF-1 cells were here investigated. Activation of signal transducer and activator of transcription (STAT) 5 protein occurred in TF-1 cells incubated either with IL-3 or with HTLV-2/CMo; in addition the virus, but not IL-3, activated STAT1. The effect of HTLV-2 required several hours, suggesting dependence on the induction of cellular factors. By screening a panel of secreted factors, granulocyte macrophage-colony-stimulating factor (GM-CSF), interferon (IFN)-gamma, and stem cell factor (SCF) were found induced by HTLV-2 in TF-1 cells. Of note is the fact that these molecules induce a variety of biologic effects through the activation of STAT proteins, including STAT1 and STAT5. Neutralization experiments indicated that GM-CSF and IFN-gamma, but not SCF, were responsible for HTLV-2-induced STAT activation, whereas anti-GM-CSF antibodies greatly inhibited TF-1 cell proliferation. Finally, incubation of BMo virus with anti-**HLA-DR** mAb rescued TF-1 cell survival in the absence of IL-3. Thus, HTLV-2 interaction with CD34(+) precursor cells may lead to the expression of cytokines that, by inducing autocrine activation of STATs, may influence the host's regenerative capacity and immune response to HTLV-2 and to other **infectious agents.**

L17 ANSWER 15 OF 59 MEDLINE on STN

2002738464. PubMed ID: 12501922. Genetic basis of tuberculosis susceptibility in India. Shanmugalakshmi S; Pitchappan R M. (University of Excellence in Genomic Sciences, Madurai, India.) Indian journal of pediatrics, (2002 Nov) 69 Suppl 1 S25-8. Journal code: 0417442. ISSN: 0019-5456. Pub. country: India. Language: English.

AB Tuberculosis is a complex disease resulting from the responses of immunological, genetic and environmental factors to the chronic **infectious agent**, Mycobacterium tuberculosis. Several genetic factors have been implicated in host disease susceptibility and the prevalence of a disease in a population may be equal to the product of the frequencies of the susceptible alleles present in the population living in an endemic area. The endogamous, sympatrically isolated gene pools, exposed to the highly infectious environmental load of India, is an ideal model to study tuberculosis susceptibility. Our recent studies in this endemic region have reiterated the association of HLA-DRB1*02 and its subtype DRB1*1501 with tuberculosis susceptibility and have identified an IL-10 associated disease susceptibility in HLAnon-DRB1*02, BCG scar negative individuals and a skewed usage of TCR Vb in BCG scar negative, HLA high risk allele carrying individuals. This indicates that there may be several pathways leading to disease. Tuberculosis susceptibility is not thus a one-gene one product manifestation but multifactorial and epistatic influences of various factors finally lead to the disease. We review the factors that has been explored under Indian context in tuberculosis susceptibility.

L17 ANSWER 16 OF 59 EMBASE

2003001287 EMBASE Genetic basis of tuberculosis susceptibility in India.
Shanmugalakshmi S.; Pitchappan R.M.. Dr. R.M. Pitchappan, Department of Immunology, Madurai Kamaraj University, Univ. of Excellence in Genomic Sci., Madurai - 625021, India. pitchappanrm@yahoo.co.uk. Indian Journal of Pediatrics Vol. 69, No. SUPPL. 1, pp. S25-S28 1 Nov 2002.
Refs: 28.
ISSN: 0019-5456. CODEN: IJPEA2
Pub. Country: India. Language: English. Summary Language: English.

ED Entered STN: 20030109

AB Tuberculosis is a complex disease resulting from the responses of immunological, genetic and environmental factors to the chronic **infectious agent**, Mycobacterium tuberculosis. Several genetic factors have been implicated in host disease susceptibility and the prevalence of a disease in a population may be equal to the product of the frequencies of the susceptible alleles present in the population living in an endemic area. The endogamous, sympatrically isolated gene

pools, exposed to the highly infectious environmental load of India, is an ideal model to study tuberculosis susceptibility. Our recent studies in this endemic region have reiterated the association of HLA-DRB1*02 and its subtype DRB1*1501 with tuberculosis susceptibility and have identified an IL-10 associated disease susceptibility in HLAnon-DRB1*02, BCG scar negative individuals and a skewed usage of TCR Vb in BCG scar negative, HLA high risk allele carrying individuals. This indicates that there may be several pathways leading to disease. Tuberculosis susceptibility is not thus a one-gene one product manifestation but multifactorial and epistatic influences of various factors finally lead to the disease. We review the factors that has been explored under Indian context in tuberculosis susceptibility.

L17 ANSWER 17 OF 59 EMBASE

2001376379 EMBASE Mechanisms for the induction of autoimmunity by **infectious agents.** Wucherpfennig K.W.. K.W. Wucherpfennig, Department of Cancer Immunology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, United States. Kai_Wucherpfennig@dfci.harvard.edu. Journal of Clinical Investigation Vol. 108, No. 8, pp. 1097-1104 2001.
Refs: 48.
ISSN: 0021-9738. CODEN: JCINAO
Pub. Country: United States. Language: English.

ED Entered STN: 20011115
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L17 ANSWER 18 OF 59 SCISEARCH

2001:443882 The Genuine Article (R) Number: 437BP. Peptide vaccines and peptide libraries. Wiesmuller K H (Reprint); Fleckenstein B; Jung G. EMC Microcollect GmbH, Sindelfinger Str 3, D-72070 Tubingen, Germany (Reprint); EMC Microcollect GmbH, D-72070 Tubingen, Germany; Univ Tubingen, Inst Organ Chem, D-72076 Tubingen, Germany. BIOLOGICAL CHEMISTRY (APR 2001) Vol. 382, No. 4, pp. 571-579. ISSN: 1431-6730. Publisher: WALTER DE GRUYTER & CO, GENTHINER STRASSE 13, D-10785 BERLIN, GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Synthetic immunogens, containing built-in adjuvanticity, B cell, T helper cell and CTL epitopes or mimotopes, are ideal and invaluable tools to study the immune response with respect to antigen processing and presentation. This serves as a basis for the development of complete and minimal vaccines which do not need large carrier proteins, further adjuvants, liposome formulations or other delivery systems.

Combinatorial peptide libraries, either completely random or characterized by one or several defined positions, are useful tools for the identification of the critical features of B cell epitopes and of MHC class I and class II binding natural and synthetic epitopes. The complete activity pattern of an O/X-n library with hundreds of peptide collections, each made up from billions of different peptides, represents the ranking of amino acid residues mediating contact to the target proteins of the immune system. Combinatorial libraries support the design of peptides applicable in vaccination against **infectious agents** as well as therapeutic tumour vaccines.

Using the principle of lipopeptide vaccines, strong humoral and cellular immune responses could be elicited. The lipopeptide vaccines are heat-stable, non-toxic, fully biodegradable and can be prepared on the basis of minimized epitopes by modern methods of multiple peptide synthesis. The lipopeptides activate the antigen-presenting macrophages and B cells and have been recently shown to stimulate innate immunity by specific interaction with receptors of the Toll family.

L17 ANSWER 19 OF 59 MEDLINE on STN

2001476831. PubMed ID: 11519856. Brain glioma and human leukocyte antigens (HLA)--is there an association. Machulla H K; Steinborn F; Schaaf A;

Heidecke V; Rainov N G. (Department GHATT, Institute of Medical Immunology, Halle (Saale), Germany.) Journal of neuro-oncology, (2001 May) 52 (3) 253-61. Journal code: 8309335. ISSN: 0167-594X. Pub. country: Netherlands. Language: English.

AB Expression of human leukocyte antigens (HLA) is important for the immune response against **infectious agents** and malignant cells. Association of single HLA antigens or HLA haplotypes with disease has been investigated previously, and positive correlations between HLA and some cancers, such as cervical or nasopharyngeal carcinomas have been reported. In the present study, HLA antigen frequencies of 65 adult Caucasian patients with low-grade, anaplastic, or malignant astrocytic glioma (WHO grades II-IV) were compared with 157 racially similar, asymptomatic control individuals. Both standard serologic and PCR techniques for HLA typing were employed for all patients and controls. Our results suggest a positive association between single HLA antigens and presence of symptomatic cerebral glioma. Compared with the control population, patients positive for HLA-A*25 had a 3.0-fold increased risk of glioma ($p = 0.04$), patients positive for HLA-B*27, a 2.7-fold risk ($p = 0.03$), and patients positive for HLA-DRB1*15, a 2.2-fold risk ($p = 0.03$), whereas HLA-DRB1*07 was associated with a 0.4-fold decreased risk of glioma ($p = 0.02$). Occurrence rate of some HLA antigen combinations and estimated haplotypes was also different in glioma patients. Thus, HLA-DRB1*15:DRB5*(51) occurrence in combination with HLA-DRB1*11 was associated with a 13.4-fold increased risk of glioma ($p = 0.001$), and the incidence of HLA-Cw*6:DRB1*07 with a 0.2-fold decreased risk of glioma ($p = 0.03$). In conclusion, single HLA antigens and their combinations and estimated haplotypes are possibly significantly more or less frequent in persons developing symptomatic cerebral glioma during their adult life, compared with asymptomatic individuals.

L17 ANSWER 20 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN

2000:790356 Document No. 133:340273 Methods and formulations for targeting **infectious agents** bearing host cell proteins. Bergeron, Michel G.; Desormeaux, Andre; Tremblay, Michel J. (Infectio Recherche Inc., Can.). PCT Int. Appl. WO 2000066173 A2 20001109, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-CA469 20000503. PRIORITY: CA 1999-2270600 19990503.

AB A formulation is disclosed for the treatment of diseases caused by an **infectious agent** which acquires host membranes protein during its life cycle. The formulation is a targeting pharmaceutical composition It comprises a ligand capable of binding the host membrane proteins coupled to a lipid-comprising vesicle, which may comprise or not a drug effective in the treatment of the disease. Specific liposomes bearing anti-**HLA-DR** or anti-CD4 antibodies comprising or not antiviral drugs, namely anti-HIV drugs, are disclosed and claimed. A method of formulation as well as a method of using the formulation in the treatment of a disease are also disclosed.

L17 ANSWER 21 OF 59 MEDLINE on STN DUPLICATE 7

2000390220. PubMed ID: 10880386. Human decidua contains potent immunostimulatory CD83(+) dendritic cells. Kammerer U; Schoppet M; McLellan A D; Kapp M; Huppertz H I; Kampgen E; Dietl J. (Department of Obstetrics and Gynecology, University of Wurzburg, Germany.. frak057@mail.uni-wuerzberg.de) . American journal of pathology, (2000 Jul) 157 (1) 159-69. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB Dendritic cells (DCs) are sentinel cells of the immune system important in initiating antigen-specific T-cell responses to microbial and

transplantation antigens. DCs are particularly found in surface tissues such as skin and mucosa, where the organism is threatened by **infectious agents.** The human decidua, despite its proposed immunosuppressive function, hosts a variety of immunocompetent CD45 cells such as natural killer cells, macrophages, and T cells. Here we describe the detection, isolation, and characterization of CD45(+), CD40(+), **HLA-DR**(++), and CD83(+) cells from human early pregnancy decidua with typical DC morphology. CD83(+) as well as CD1a(+) cells were found in close vicinity to endometrial glands, with preference to the basal layer of the decidua. In vitro, decidual CD83(+) cells could be enriched to approximately 30%, with the remainder of cells encompassing DC-bound CD3(+) T cells. Stimulation of allogeneic T cells in a mixed leukocyte reaction by the decidual cell fraction enriched for CD83(+) cells, was similar to that obtained with blood monocyte-derived DCs, demonstrating the potent immunostimulatory capacity of these cells. Decidual DCs with morphological, phenotypic, and functional characteristics of immunostimulatory DCs might be important mediators in the regulation of immunological balance between maternal and fetal tissue, leading to successful pregnancy.

L17 ANSWER 22 OF 59 MEDLINE on STN DUPLICATE 8
1999138891. PubMed ID: 9973468. Use of antagonist peptides to inhibit in vitro T cell responses to Par j1, the major allergen of Parietaria judaica pollen. De Palma R; Wu S; Sallusto F; Di Felice G; Martucci P; Geraci D; Colombo P; Troise C; Sacerdoti G; Nocera A; Gorski J. (Dipartimento di Internistica Clinica e Sperimentale II Universita' di Napoli, Italy.) Journal of immunology (Baltimore, Md. : 1950), (1999 Feb 15) 162 (4) 1982-7. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Antigenic peptides with substituted side chains inhibit immune responses to a number of recall Ags from **infectious agents** in vitro. Here we show that the same strategy can be applied to peptides derived from a pollen protein, the major allergen of Parietaria judaica(Par j1), a plant responsible for most allergenic sensitization in the southern Mediterranean area. Three T cell lines responding to Par j1 protein were used to identify a stimulatory peptide. Two different monosubstituted altered peptide ligands (APL) were identified that bound to the **HLA-DR** of the responders, did not stimulate the T cell lines on their own, and decreased the response to subsaturating amounts of the unmodified stimulatory peptide. Most important, these APL were able to inhibit the response of these cell lines to intact Par j1 protein. A third monosubstituted peptide bound to the **HLA-DR** but did not show inhibitory activity. The two APL had a lower affinity than the unsubstituted peptide for the **HLA-DR** . The last two observations make MHC blockade an unlikely explanation for the observed effect. These results indicate the action of a specific peptide-mediated antagonism that may be useful in controlling the T cell component of an allergic response.

L17 ANSWER 23 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
2000:11573 Document No. 132:136164 MHC class II tetramers identify peptide-specific human CD4+ T cells proliferating in response to influenza A antigen. Novak, Erik J.; Liu, Andrew W.; Nepom, Gerald T.; Kwok, William W. (Benaroya Research Institute, Virginia Mason Research Center, Seattle, WA, 98101, USA). Journal of Clinical Investigation, 104(12), R63-R67 (English) 1999. CODEN: JCINAO. ISSN: 0021-9738. Publisher: American Society for Clinical Investigation.

AB Antigen-specific T helper cells present in peripheral blood at very low frequencies are capable of rapid clonal expansion during antigenic challenge. The exquisite specificity of this response provides for activation and expansion of a very select cohort of T cells, a feature we have used to directly identify and quantify human epitope-specific T helper cells from peripheral blood. Soluble tetramerized class II MHC mols., loaded with an immunodominant peptide from hemagglutinin (HA) and labeled with fluorescent dyes, were constructed and used to directly identify

antigen-specific T cells from influenza-immune individuals. After 7 days of proliferation in response to stimulation by HA peptide or whole influenza vaccine, cells staining pos. with the HA tetramer had undergone between 6 and 9 divisions and were CD3+, CD4+, CD25+, and CD8-, characteristic of activated T helper cells responding to antigen. The HA epitope-specific component of the complex response to whole influenza vaccine represented a major subset of proliferating T helper cells. Soluble class II tetramers allow a direct approach for the anal. of immunodominant antigenic specificities. The identification of antigen-specific T helper cells in the peripheral blood provides a means for tracking the immune response against **infectious agents** and in autoimmune disease.

L17 ANSWER 24 OF 59 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN DUPLICATE 9

1999255196 EMBASE The contribution of inducible nitric oxide and cytomegalovirus to the stability of complex carotid plaque. Hunter G.C.; Henderson A.M.; Westerband A.; Kobayashi H.; Suzuki F.; Yan Z.- Q.; Sirsjo A.; Putnam C.W.; Hansson G.K.; Krupski W.. Dr. G.C. Hunter, Department of Surgery, Univ. of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555-0541, United States. Journal of Vascular Surgery Vol. 30, No. 1, pp. 36-50 1999.

Refs: 44.

ISSN: 0741-5214. CODEN: JVSUES

Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 19990812

AB Background: Although the association between inflammation and atherosclerosis is well established, the biologic events that trigger the local inflammatory response within plaque are not fully understood. Cytotoxic free radicals and **infectious agents**, both of which are associated with an inflammatory response, have previously been implicated in the initiation and progression of atherosclerosis. In this study, we analyzed carotid plaque for evidence of oxidative vascular injury by determining the presence and distribution of inducible nitric oxide synthase (iNOS) expression and nitrotyrosine formation and for evidence of infection with cytomegalovirus. Methods: Carotid plaque from 51 patients who underwent endarterectomy for either primary (n = 37) or recurrent (n = 14) stenosis were examined histologically (hematoxylineosin staining and Masson's trichrome staining) and with immunohistochemistry with specific antibodies to α-smooth muscle actin, macrophages (CD68), T-lymphocytes (CD3), and T-cell activation (human leukocyte antigen-DR). Twenty-eight specimens from patients with primary (n = 15) and recurrent (n = 13) stenosis were examined for the presence of iNOS and nitrotyrosine with immunohistochemistry and in situ hybridization (iNOS). Twenty-three additional specimens (22 primary, and 1 recurrent) were analyzed with antibodies to p53, cytomegalovirus, and the polymerase chain reaction (cytomegalovirus, n = 8). Results: Primary atherosclerotic lesions were either complex heterogenous cellular plaques (n = 29) or relatively acellular fibrous plaques (n = 8). Ten of 14 recurrent plaques were either complex or fibrous lesions, and the remaining four were typical of myointimal thickening. CD68-positive staining cells were detected in all specimens regardless of their structural morphology. CD3-positive cells were interspersed between macrophages in all heterogeneous cellular plaques and only infrequently noted in fibrous plaques, iNOS and nitrotyrosine immunoreactivity were detected in macrophages and smooth muscle cells in all complex and fibrous plaques and in two of four myointimal plaques. The presence of iNOS and nitrotyrosine in plaque correlated with the existence of symptoms in 80% of primary and 62% of recurrent lesions. Cytomegalovirus was detected in only two of 23 carotid specimens (9%). Conclusion: The association between ischemic cerebrovascular symptoms and iNOS and nitrotyrosine immunoreactivity in complex primary and recurrent carotid plaque and the infrequent occurrence of cytomegalovirus in primary carotid lesions suggests that ongoing free radical oxidative damage rather than viral infection may contribute to plaque instability in patients with complex and fibrous carotid plaques.

L17 ANSWER 25 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
1998:424096 Document No. 129:94451 Superantigen based methods and compositions for treatment of diseases. Terman, David S. (Terman, David S., USA). PCT Int. Appl. WO 9826747 A2 19980625, 140 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US23637 19971217. PRIORITY: US 1996-33172 19961217; US 1997-44074 19970417.

AB The present invention relates to therapeutic methods and compns. employing superantigens. Methods and compns. employing superantigens and immunotherapeutic proteins in combination with one another have been found to provide more effective treatment than either component used alone. Superantigens, in conjunction with one or more addnl. immunotherapeutic antigens, may be used to either induce a therapeutic immune response directed against a target or to inhibit a disease causing immune response. Specific combinations of superantigens and immunotherapeutic antigens are used to treat specific diseases. The induction (or augmentation) of a desired immune against a target may be used, for example, to kill cancer cells or kill the cells or an **infectious agent.** The inhibition of an immune response, e.g., through the induction of T cell anergy, may be used to reduce the symptoms of an autoimmune disease. Diseases that may be treated by the methods and compns. of the invention include neoplastic diseases, infectious diseases, and autoimmune diseases. One aspect of the invention is to provide methods for the treatment of diseases comprising the steps of administering an effective amount of a superantigen and an immunotherapeutic so as to have the desired therapeutic effect. The superantigen and immunotherapeutic antigen may be administered together as a mixture Alternatively, the superantigen and immunotherapeutic antigen may be administered sep. In one embodiment of the invention, the superantigen and immunotherapeutic antigen are administered to the patient in the form of a immunotherapeutic antigen-superantigen polymer of the invention. Another aspect of the invention is to provide methods for the treatment of diseases comprising the steps of incubating a lymphocyte population ex vivo a superantigen and an immunotherapeutic protein so as to either activate or anergize T cells within the selected population.

L17 ANSWER 26 OF 59 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
1998350756 EMBASE Molecular mimicry and immune-mediated diseases. Oldstone M.B.A.. M.B.A. Oldstone, Viral Immunobiology Laboratory, Division of Virology, Scripps Research Institute, 10550 N. Torrey Pines Road, San Diego, CA 92037, United States. mbaobo@scripps.edu. FASEB Journal Vol. 12, No. 13, pp. 1255-1265 1998.
Refs: 102.
ISSN: 0892-6638. CODEN: FAJOEC
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 19981109

AB Molecular mimicry has been proposed as a pathogenetic mechanism for autoimmune disease, as well as a probe useful in uncovering its etiologic agents. The hypothesis is based in part on the abundant epidemiological, clinical, and experimental evidence of an association of **infectious agents** with autoimmune disease and observed cross-reactivity of immune reagents with host 'self' antigens and microbial determinants. For our purpose, molecular mimicry is defined as similar structures shared by molecules from dissimilar genes or by their protein products. Either the molecules' linear amino acid sequences or their conformational fits may be shared, even though their origins are as separate as, for example, a virus and a normal host-self determinant. An immune response against the determinant shared by the host and virus can evoke a tissue-specific immune response that is presumably capable of eliciting cell and tissue destruction. The probable mechanism is generation of cytotoxic cross-reactive effector lymphocytes or antibodies that recognize specific determinants on target cells. The induction of

cross- reactivity does not require a replicating agent, and immune-mediated injury can occur after the immunogen has been removed - a hit-and-run event. Hence, the viral or microbial infection that initiates the autoimmune phenomenon may not be present by the time overt disease develops. By a complementary mechanism, the microbe can induce cellular injury and release self antigens, which generate immune responses that cross-react with additional but genetically distinct self antigens. In both scenarios, analysis of the T cells or antibodies specifically engaged in the autoimmune response and disease provides a fingerprint for uncovering the initiating **infectious agent.**

L17 ANSWER 27 OF 59 MEDLINE on STN DUPLICATE 10
1998409043. PubMed ID: 9738663. Interferon-alpha and granulocyte-macrophage colony-stimulating factor differentiate peripheral blood monocytes into potent antigen-presenting cells. Paquette R L; Hsu N C; Kiertscher S M; Park A N; Tran L; Roth M D; Glaspy J A. (Department of Medicine, the University of California at Los Angeles, 90095-1678, USA.. paquette@ucla.edu) . Journal of leukocyte biology, (1998 Sep) 64 (3) 358-67. Journal code: 8405628. ISSN: 0741-5400. Pub. country: United States. Language: English.

AB The diverse roles of interferon-alpha (IFN-alpha) in regulating the immune response to **infectious agents** suggested that it might affect dendritic cell (DC) development. Peripheral blood mononuclear cells cultured with IFN-alpha and granulocyte-macrophage colony-stimulating factor (GM-CSF) developed a dendritic morphology and expressed high levels of the class I and II human leukocyte antigens (HLA), B7 co-stimulatory molecules, adhesion proteins, and CD40. Elevated DC expression of B7-2 and **HLA-DR** was observed with increasing IFN-alpha concentrations up to 5000 U/mL. The effects of IFN-alpha on DC immunophenotype were not reversed by adding neutralizing antibodies against interleukin-4 (IL-4) or tumor necrosis factor alpha to the cell cultures or by eliminating lymphocytes from the cultures. The addition of IFN-alpha to cultures containing optimal concentrations of IL-4 and GM-CSF significantly increased the B7-2 and **HLA-DR** levels above those present on DCs grown in two cytokines. The DCs generated with IFN-alpha and GM-CSF were potent antigen-presenting cells in allogeneic mixed leukocyte reactions. They also were capable of taking up, processing, and presenting tetanus toxin to autologous T lymphocytes. These results demonstrate an important role for IFN-alpha in the generation of DCs with potent antigen-presenting capabilities from peripheral blood monocytes.

L17 ANSWER 28 OF 59 MEDLINE on STN DUPLICATE 11
1999155659. PubMed ID: 10036634. HLA-DRB1 motifs and heat shock proteins in rheumatoid arthritis. Auger I; Toussirot E; Roudier J. (Laboratoire d'immunorhumatologie, Faculte de medecine, Marseille, France.) International reviews of immunology, (1998) 17 (5-6) 263-71. Ref: 23. Journal code: 8712260. ISSN: 0883-0185. Pub. country: Switzerland. Language: English.

AB Susceptibility to develop Rheumatoid arthritis (RA) maps to a highly conserved amino acid motif expressed in the third hypervariable region of different HLA-DRB1 alleles. This motif, namely QKRAA, QRRAA or RRRAA helps the development of RA by an unknown mechanism. In the past ten years, we have extensively studied the unique properties of the QKRAA motif of HLA-DRB1*0401 and have found: (1) That it can constitute B and T cell epitopes on many **infectious agents**; (2) That it can shape the T cell repertoire; (3) That it is overrepresented in protein databases; (4) That it constitutes a binding motif for the highly conserved family of 70 kD heat shock proteins. This may cause abnormal trafficking of HLA-DRB1*0401 in B cells and/or abnormal T cell responses to bacterial and human 70 kD heat shock proteins in people who express HLA-DRB1*0401.

L17 ANSWER 29 OF 59 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1998:307785 The Genuine Article (R) Number: ZH754. Relationship between HLA antigens and **infectious agents** in contributing towards the development of Graves' disease. Kraemer M H S (Reprint); Donadi E A; Tambascia M A; Magna L A; Prigenzi L S. Rua Gustavo Rodrigues Doria 255, BR-13083060 Campinas, SP, Brazil (Reprint); UNICAMP, Dept Clin Pathol, Lab Transplantat Immunogenet, Campinas, SP, Brazil; UNICAMP, Dept Internal Med, Campinas, SP, Brazil; UNICAMP, Sch Med Sci, Dept Genet, Campinas, SP, Brazil; Sch Med, Dept Internal Med, Div Clin Immunol, Ribeirao Preto, SP, Brazil. IMMUNOLOGICAL INVESTIGATIONS (1998) Vol. 27, No. 1-2, pp. 17-29. ISSN: 0882-0139. Publisher: MARCEL DEKKER INC, 270 MADISON AVE, NEW YORK, NY 10016 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Graves' disease (GD) is an autoimmune thyroid disorder which is associated with the human leucocyte antigens HLA-DR3 and DQA1* 0501 in Caucasians. We have explored the possibility that some patients with certain HLA specificities develop anti-HLA antibodies which are correlated with environmental factors that may contribute to the development of GD. We studied 40 GD patients and 157 healthy individuals (controls). Serology was used to type HLA-A -B, -Cw, and -DR antigens. The frequencies of these antigens in relation to lymphocytotoxic anti-HLA-A-B-Cw-DR antibodies and two environmental factors (Yersinia enterocolitica and Coxsackie B virus) were determined. The frequencies of HLA-B15, -B21 and DR3 antigens were increased, whereas **HLA-DRS** antigen was decreased in GD patients. A significant association between HLA-DR3 antigen and lymphocytotoxic antibodies was observed, i. e., IgGs from GD patients were cytotoxic to HLA-DR3+ normal B cells. Following absorption with Yersinia enterocolitica or Coxsackie-B-virus, only Coxsackie-B virus completely inhibited the lymphocytotoxic reactions against HLA-DR3(+) B cells. Besides confirming the association of HLA-DR3 with GD, this study also suggests the role of Coxsackie-reative HLA-DR3 antibodies as contributing factors to the pathogenesis of the disease.

L17 ANSWER 30 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN

1997:503461 Document No. 127:120708 Use of immunoconjugates to enhance the efficacy of multi-stage cascade boosting vaccines. Hansen, Hans J. (Immunomedics, Inc., USA; Hansen, Hans J.). PCT Int. Appl. WO 9723237 A1 19970703, 51 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US19755 19961220. PRIORITY: US 1995-577106 19951222.

AB Humoral and cellular immune responses against tumor cells and **infectious agents** are induced in a mammal using a vaccine comprising immunoconjugates that comprise antibodies and anti-idiotype antibodies that mimic an epitope of an antigen that is associated with a tumor or an **infectious agent.** These immunoconjugates also comprise a peptide that contains an epitope of a tumor associated antigen or **infectious agent** antigen, a peptide that contains a minimal recognition unit of an anti-idiotype antibody, or a peptide that induces a strong major histocompatibility complex-restricted immune response. Antibodies and cytokines also may be used to amplify the immune cascade. As an example, to target carcinoembryonic antigen (CEA)-expressing tumor cells, the A3B3 epitope of CEA is produced recombinantly or by peptide synthesis using the known amino acid sequence. A3B3 peptides are conjugated to IMMU-LL1 antibody (a monoclonal antibody that binds to the **HLA-DR** complex on various immunocytes) or fragments using standard techniques. The IMMU-LL1-A3B3 vaccine is administered s.c. to induce the immune response against CEA-bearing tumor cells. The vaccine also can be administered i.v. to boost the immune response against such tumor cells.

L17 ANSWER 31 OF 59 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1997:20054 The Genuine Article (R) Number: VZ128. In vivo functions mediated by the p41 isoform of the MHC class II-associated invariant chain. Takaesu N T (Reprint); Lower J A; Yelon D; Robertson E J; Bikoff E K. HARVARD UNIV, DEPT MOL & CELLULAR BIOL, BIOL LABS, CAMBRIDGE, MA 02138. JOURNAL OF IMMUNOLOGY (1 JAN 1997) Vol. 158, No. 1, pp. 187-199. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We used a ''hit and run'' gene targeting strategy to generate mice expressing only the p41 isoform of the conserved invariant (Ii) chain associated with MHC class II molecules, In contrast to mutants expressing only p31 Ii chain, a small proportion of A alpha(b)A beta(b) molecules produced by these animals have reduced mobilities in SDS-PACE and appear incompletely processed, Nonetheless, class II surface expression, peptide occupancy, CD4(+) T cell maturation, and proliferative responses toward intact protein Ags are efficiently reconstituted, Moreover, spleen cells exclusively expressing p41 or p31 alone display equivalent dose-response curves in Ag presentation assays, Similar conclusions were reached analyzing mutants expressing two independent MHC haplotypes, Overall, these results demonstrate that Ii chain functional activities as a class II-specific chaperone are largely shared by p31 and p41 isoforms in the intact animal, Mutant mouse strains producing only p31 or p41 under control of endogenous regulatory elements responsible for constitutive and inducible Ii chain expression should prove useful for dissecting the contributions of these isoforms to diverse CD4(+) T cell responses in vivo, such as those responsible for Ab production, inflammatory responses, autoimmune diseases, and protection against **infectious agents.**

L17 ANSWER 32 OF 59 MEDLINE on STN

97411449. PubMed ID: 9266427. Genetics of multiple sclerosis--how could disease-associated HLA-types contribute to pathogenesis?. Martin R. (Department of Neurology, University of Tubingen Medical School, Federal Republic of Germany.) Journal of neural transmission. Supplementum, (1997) 49 177-94. Ref: 89. Journal code: 0425126. ISSN: 0303-6995. Pub. country: Austria. Language: English.

AB Multiple sclerosis is a chronic demyelinating disease of the central nervous system in young adults. It is considered a T cell-mediated autoimmune disease which is probably triggered by exogenous events, e.g. **infectious agents**, in susceptible individuals. Population, family and twin studies indicate that genetic factors and most likely several genes are associated with disease, but it is clear from the concordance rates of identical twins (25-30%) that genetic background as well as exogenous or somatic events are required to develop disease. Among many candidate genes which have been analyzed during recent years, the strongest association was shown for genes of the HLA-class II complex, in particular HLA-DR15 Dw2 and -DQw6. At present, it is not clear how the expression of a particular HLA-class II gene translates into susceptibility to develop an organ-specific autoimmune disease. Potential explanations how this could occur will be discussed.

L17 ANSWER 33 OF 59 MEDLINE on STN

1998101106. PubMed ID: 9438209. The CCR5 deletion mutation fails to protect against multiple sclerosis. Bennetts B H; Teutsch S M; Buhler M M; Heard R N; Stewart G J. (Department of Clinical Immunology, Westmead Hospital, NSW, Australia.. bruceb@westmed.wh.usyd.edu.au) . Human immunology, (1997 Nov) 58 (1) 52-9. Journal code: 8010936. ISSN: 0198-8859. Pub. country: United States. Language: English.

AB Recent advances in the understanding and identification of chemokines and their receptors have provided evidence for their consideration as candidate loci with respect to genetic susceptibility/resistance to MS. Increased levels of the chemokine, macrophage inflammatory protein (MIP)-1 alpha, have been demonstrated in the cerebrospinal fluid of both patients

with MS and mice with EAE, and anti-MIP-1 alpha antibodies have been shown to prevent EAE. Recently, a common deletion mutation in the gene for the major receptor for MIP-1 alpha, chemokine receptor 5 (CCR5) has been described. Homozygotes for the mutation fail to express this receptor. Moreover, homozygotes are highly protected against HIV infection this has potential implications for the cell entry of **infectious agents** in other multifactorial disease where a viral component may be involved. In view of these aspects, a group of 120 unrelated Australian relapsing remitting MS and 168 unrelated control subjects were screened for the CCR5 delta 32 mutation. There was no significant difference in the allele frequency of CCR5 delta 32 gene between the MS patients (0.1125) and the control population (0.0921). The presence of two CCR5 delta 32 homozygotes in the MS patients indicates that the absence of CCR5 is not protective against MS. These data suggest that CCR5 is not an essential component in MS expression, though this may be due to redundancy in the chemokine system where different chemokine receptors may substitute for CCR5 when it is absent.

L17 ANSWER 34 OF 59 MEDLINE on STN

97384058. PubMed ID: 9239904. [Insulin-dependent diabetes mellitus in Santiago, Chile: the role of immunogenetic and environmental factors]. Diabetes mellitus insulino-dependiente en Santiago de Chile: rol patogenetico de factores inmunogeneticos y ambientales. Perez F; Calvillan M; Santos J L; Carrasco E. (Grupo de Biologia Moleculary, Universidad de Chile, Santiago, Chile.) Revista medica de Chile, (1996 Oct) 124 (10) 1177-86. Journal code: 0404312. ISSN: 0034-9887. Pub. country: Chile. Language: Spanish.

AB The role of HLA class II alleles in the genetic susceptibility to develop insulin-dependent diabetes mellitus (IDDM) was examined by means of PCR and oligospecific probes in 63 IDDM children and 74 controls subjects. In diabetic patients we found a significant increase in the alleles frequency DR3, DR4, DQB1*0302 and DQA1*0301 compared to the control group, where the most prevalent alleles were DR2, DR14 (DRB1*1402), DQA1*0101 and DQA1*0201. All the risk genotypes in the diabetic group were similar than in other caucasian groups: DR3/DR4-DQB1*0201/0302-DQA1*0301/0501 and DR4/DR4-DQB1*0302/0302-DQA1*0301/0301. The homozygote character no asp57 conferred an absolute risk (AR) of 3.87 and the marker Arg52 an AR of 5.78/100.000 bab year. The homozygosis for both markers (no Asp57 + Arg52) had an AR of 7.56/100.000 bab year. Regarding environmental factors associated with IDDM, our population under study showed a low prevalence of **infectious agents** (mainly mumps and rubella, specifically associated with IDDM) and a high prevalence of effective breast-feeding (over 3 months). These factors could be exercising a protector role in the development of IDDM. The factors that appear to be important in the low incidence of IDDM in Santiago de Chile are: the low prevalence of **infectious agents** related to IDDM, the high percentage of breast-feeding children in the population, the reduced frequency of susceptible molecules as DR3, DQB1*0201 (compared to other caucasian groups) and the presence of protective genotypes related to DR13 and DR14 observed in the non-diabetic children.

L17 ANSWER 35 OF 59 EMBASE

96143174 EMBASE Document No.: 1996143174. Retroviruses and bone diseases. Labat M.-L.. LPODC, Institut Biomedical des Cordeliers, 15, rue de l'Ecole de Medecine,75270 Paris Cedex 06, France. Clinical Orthopaedics and Related Research No. 326, pp. 287-309 1996.
ISSN: 0009-921X. CODEN: CORTBR
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 960604

AB In 1980, retroviruses were shown to be pathogenic to humans, and experimentation on animals involving retroviruses an causal agents of tumors and degenerative diseases of bone, brain, and lung gained interest. Osteopetrosis, which can be either inherited in rodents or retrovirally induced in cats, is exemplary. Because of replication cycle, retroviruses

can be propagated not only as **infectious agents** but also as cellular genes. If a retroviral infection occurs in germ line cells, the viral genes, which must integrate in the host's DNA, can be passed on to the progeny and inherited as Mendelian characteristics. Therefore, a retroviral etiology could account for diseases that present either an sporadic (infectious) or familial (inherited), although they may be similar in their clinical manifestations. This approach led to the finding of 2 new human retroviruses: 1 in a patient who had sporadic benign osteopetrosis, and the other in a patient who had sporadic paraarticular osteoma. In both patients, the retrovirus was isolated from mononuclear blood cells, not from bone cells, because of the links between bone and the immune system. A systematic search for retroviruses in patients who have sporadic bone disease, which also may appear as inherited disease, has yet to be performed. Patients with sporadic disease could be managed by antiretroviral agents such as Zidovudin.

L17 ANSWER 36 OF 59 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

97158294 EMBASE Document No.: 1997158294. HLA and paget's disease of bone. Grosso P.; Santalena G.; Fare M.; Mercuriali F.; Cherie-Ligniere G.. G. Cherie-Ligniere, Via Cesare, Correnti 17, 20123 Milano, Italy. Italian Journal of Mineral and Electrolyte Metabolism Vol. 10, No. 3-4, pp. 165-167 1996.
Refs: 14.
ISSN: 1121-1709. CODEN: IMEMEU
Pub. Country: Italy. Language: English. Summary Language: English.

ED Entered STN: 970612

AB The aetiology of Paget's disease of bone is unknown; many theories have been proposed in the literature in these years: one of the most interesting and important, suggests that in some families the disorder may be hereditary. However many problems are still to be solved such as: the role of an inherited susceptibility to an **infectious agent** and how it can explain the late onset of the disease; the differences between data obtained trough preliminary studies on HLA linkage in families with Paget's disease. For this reason, in the present study, we have examined the correlation between HLA Class I and Class II antigens and Paget's disease by recruiting 16 patients, affected by this disease. Six patients, carrying an uncommon genetic arrangement were further analyzed by a molecular biology PCR-SSP method according to Olerup for the typing of DR and DQ loci.

L17 ANSWER 37 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN

1996:608417 Document No. 125:245038 Phenotypic analysis of antigen-specific T lymphocytes. Altman, John D.; Moss, Paul A. H.; Goulder, Philip J. R.; Barouch, Dan H.; McHeyzer-Williams, Michael G.; Bell, John I.; McMichael, Andrew J.; Davis, Mark M. (Sch. Medicine, Stanford Univ., Stanford, CA, 94305-5428, USA). Science (Washington, D. C.), 274(5284), 94-96 (English) 1996. CODEN: SCIEAS. ISSN: 0036-8075. Publisher: American Association for the Advancement of Science.

AB Identification and characterization of antigen-specific T lymphocytes during the course of an immune response is tedious and indirect. To address this problem, the peptide-major histocompatibility complex (MHC) ligand for a given population of T cells was multimerized to make soluble peptide-MHC tetramers. Tetramers of human lymphocyte antigen A2 that were complexes with two different human immunodeficiency virus (HIV)-derived peptides or with a peptide derived from influenza A matrix protein bound to peptide-specific cytotoxic T cells in vitro and to T cells from the blood of HIV-infected individuals. In general, tetramer binding correlated well with cytotoxicity assays. This approach should be useful in the anal. of T cells specific for **infectious agents**, tumors, and autoantigens.

L17 ANSWER 38 OF 59 MEDLINE on STN DUPLICATE 12

95347806. PubMed ID: 7622216. Shigella infection induces cellular activation of T and B cells and distinct species-related changes in

peripheral blood lymphocyte subsets during the course of the disease. Islam D; Bardhan P K; Lindberg A A; Christensson B. (Division of Clinical Bacteriology, Karolinska Institute, Huddinge University Hospital, Sweden.) Infection and immunity, (1995 Aug) 63 (8) 2941-9. Journal code: 0246127. ISSN: 0019-9567. Pub. country: United States. Language: English.

AB Immunophenotypic changes in peripheral blood lymphocytes (T, B, and NK cells) in patients during shigellosis was characterized by using triple-color flow cytometry. Eleven Shigella dysenteriae 1-infected adult patients (SDIP), 11 Shigella flexneri-infected adult patients (SFIP), 15 age- and sex-matched healthy controls from Bangladesh (C-B), and 15 healthy volunteers from Sweden (V-S) were studied. In SDIP and SFIP, a significant increase in the CD45RO+ cells in both CD4+ and CD8+ T cells were seen. We found evidence for sequential T-cell activation, as shown by increased proportions of CD25 and CD4+ cells; **HLA-DR** and CD38 on CD8+ cells, and CD54 on CD4+ and CD8+ cells. We found differences in the lymphocyte activation and subset patterns related to the infecting Shigella species. Thus, a decrease in CD45 expression was seen in SFIP; this decrease progressed further during the disease. The proportions of NK cells (CD56+ cells) and CD3- CD8+ cells out of the total CD8+ cells were increased in SFIP but not in SDIP. The CD3+ CD8+ CD57+ T-cell subset was significantly lower in SDIP than in C-B. The proportion of B-lymphocyte-expressing activation markers CD80 and CD23 was higher in patients than in C-B. There was a significant increase in the proportion of CD4+ T cells and a significant decrease in the percentages of total B cells, the CD3+ CD8+ CD57+ T-cell subset, and the CD56+ CD16+ NK-cell subset for V-S compared with C-B. Our results indicate that distinct subset changes and activation patterns are elicited in SDIP compared with SFIP and also that the degree of activation is related to disease severity. In addition, a common sequence of cell activation was seen during the disease course. The difference in the subset patterns seen in C-B and V-S may be related to differences in the levels or spectra of **infectious agents** in the environment.

L17 ANSWER 39 OF 59 MEDLINE on STN DUPLICATE 13

95383660. PubMed ID: 7655017. Hepatitis C virus within a malignant lymphoma lesion in the course of type II mixed cryoglobulinemia. De Vita S; Sansonno D; Dolcetti R; Ferraccioli G; Carbone A; Cornacchiulo V; Santini G; Crovatto M; Gloghini A; Dammacco F; Boiocchi M. (Department of Experimental Oncology 1, Centro di Riferimento Oncologico, Aviano (PN), Italy.) Blood, (1995 Sep 1) 86 (5) 1887-92. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Hepatitis C virus (HCV) has been implicated as the major etiologic factor sustaining B-cell clonal expansion in type II mixed cryoglobulinemia (MC). A putative pathogenetic role of HCV in the development of MC-associated B-cell malignancies has also been speculated. We report for the first time the localization of HCV within a parotid non-Hodgkin's lymphoma (NHL) lesion in the course of HCV-related type II essential MC, an important step to implicate any **infectious agent** in the lymphomagenesis. Plus and minus strand HCV RNA was first demonstrated by polymerase chain reaction on the whole RNA from the lesion. Further immunohistochemical studies localized HCV c22 proteins in the residual ductal or acinar parotid structures, which also abnormally expressed **HLA-DR** antigens. Weak c22 signals were inconstantly detected in cells strictly confined around the residual epithelium, while all the remaining infiltrating cells in the parotid lesion stained c-22-negative. Staining for c33 and c100 HCV antigens was negative. In situ hybridization (ISH) studies again identified the residual parotid epithelial cells as the site of HCV infection and replication in the NHL lesion. Sialotropic viruses previously involved in lymphoproliferation, ie, Epstein-Barr virus and human herpesvirus-6, were absent in the same tissue lesion. According to the current models of B-cell lymphomagenesis, a role of HCV as an exogenous antigenic stimulus should be considered for NHL development in the present case, whereas malignant B cells do not appear permissive of active HCV replication. Further efforts would be worthwhile to clarify a role of HCV infection in the development of some

B-cell malignancies.

L17 ANSWER 40 OF 59 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
95127769 EMBASE Document No.: 1995127769. Preliminary evidence of an association between HLA-DPB1*0201 and childhood common acute lymphoblastic leukaemia supports an infectious aetiology. Taylor G.M.; Robinson M.D.; Binchy A.; Birch J.M.; Stevens R.F.; Jones P.M.; Carr T.; Dearden S.; Gokhale D.A.. Immunogenetics Laboratory, St Mary's Hospital, Hathersage Road,Manchester M13 0JH, United Kingdom. Leukemia Vol. 9, No. 3, pp. 440-443 1995.
ISSN: 0887-6924. CODEN: LEUKED
Pub. Country: United Kingdom. Language: English. Summary Language: English.
ED Entered STN: 950514
AB It has been suggested that childhood leukaemia may be the abnormal outcome of a common infection. Rare events caused by common environmental events such as infections are likely to be influenced by host genetic susceptibility. We have therefore investigated whether immunogenetic susceptibility contributes to the risk of childhood common ALL (c-ALL). In this preliminary study, we report that children with c-ALL (n = 63) carry the HLA-DPB1 locus allele *0201 twice and nearly three times more frequently than adult (n = 92; relative risk (RR) = 2.9, P < 0.05) or infant controls (n = 82; RR = 2.1). Moreover, children with c-ALL are 3-4 times more likely than controls to be heterozygous for DPB1*0201/*0301, /*0401 and /*0402 (RR(adult controls) = 3.9; RR(infant controls) = 2.8) These results suggest that HLA-DPB1*0201 either alone or with other DPB1 alleles contributes to the risk of childhood c-ALL, possibly by increasing susceptibility to an **infectious agent.**

L17 ANSWER 41 OF 59 MEDLINE on STN DUPLICATE 14
96069868. PubMed ID: 7586671. Accumulation of activated CD4+ lymphocytes in the lung of individuals infected with HIV accompanied by increased virus production in patients with secondary infections. Franchini M; Walker C; Henrard D R; Suter-Gut D; Braun P; Villiger B; Suter M. (Swiss Institute of Allergy and Asthma Research (SIAF), Davos Platz, Switzerland.) Clinical and experimental immunology, (1995 Nov) 102 (2) 231-7. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The lung is continuously exposed to infectious and non-**infectious agents** causing cell activation. Activated cells in the lung such as antigen-presenting cells which harbour HIV may favour this organ as a site for virus production. To test this hypothesis, cells from blood and bronchoalveolar lavage (BAL) of HIV-infected patients and healthy controls were obtained and the activation of the cells were analysed by measuring the expression of IL-2 receptor, **HLA-DR** and VLA-1.
The HIV-infected individuals were subdivided into 'lung symptomatic' or 'lung asymptomatic' patients, depending on the presence or absence of secondary lung diseases besides HIV. All HIV-infected individuals demonstrated a decreased number of CD4+ lymphocytes in blood; however, normal numbers of these cells were found in BAL. The activation state of CD4+ and CD8+ T lymphocytes in blood and BAL was higher in lymphocytes from HIV-infected patients compared with controls. The activation state was highest in the lung symptomatic group. Lung symptomatic patients and lung asymptomatic patients with extrapulmonary infections had increased levels of free virus in plasma. Four out of four individuals without or with only low amounts of cell-free HIV in plasma belonged to the symptom-free subgroup. These results suggest that microorganisms other than HIV may promote viral replication via antigen-driven accumulation and activation of CD4+ cells in the lung or other organs, and thus may be responsible for the loss of helper T cells and the progression of the disease.

L17 ANSWER 42 OF 59 MEDLINE on STN
97122971. PubMed ID: 8968220. Multiple sclerosis: immune mechanism and

update on current therapies. Bansil S; Cook S D; Rohowsky-Kochan C. (University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark 07103, USA.) Annals of neurology, (1995 May) 37 Suppl 1 S87-101. Ref: 147. Journal code: 7707449. ISSN: 0364-5134. Pub. country: United States. Language: English.

AB Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) afflicting approximately 250,000 individuals in the United States. This inflammatory disease has variable clinical manifestations, ranging from a relapsing-remitting course to a chronic progressive disease. Approximately one third of MS patients have chronic progressive disease often leading to severe impairment of mobility, paralysis, poor vision, and disturbances of bladder and bowel function. Although the etiology and pathogenesis remain unknown, accumulating evidence supports the hypothesis that exposure to an as-yet-unidentified **infectious agent**(s) triggers an aberrant immune response against self nervous tissue in genetically susceptible individuals. The tenfold higher concordance rate for MS in monozygotic twins compared to dizygotic twins, the increased incidence of MS in women compared to men (2:1), and the familial and racial occurrence of MS provide strong evidence that genetic factors influence susceptibility to MS. The major predisposing genes in MS are the human leukocyte antigen (HLA) class II molecules, DR15 and DQw6, molecularly defined as HLA-DRB1, 1501-DQA1 0102-DQB1 0602. In certain ethnic groups, MS susceptibility is more strongly associated with other DR molecules. Environmental factors are also believed to play a role, as suggested by the unique worldwide prevalence, migration effects, and epidemiological studies. Increased serum and cerebrospinal fluid antibody titers to numerous viruses have been reported; however, there have been no confirmed studies detecting viral RNA or antigen in MS brain tissue. At the present time, no known treatment can significantly alter the progression of MS. Based on the postulate that MS is an autoimmune disease associated with abnormalities in immunoregulation, a number of different immunosuppressive and immunomodulating agents have been tested as therapeutic modalities. In this article, we review the circumstantial evidence suggesting that immune system abnormalities are associated with the disease process, and provide an update on current therapies used in MS.

L17 ANSWER 43 OF 59 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1995:117613 The Genuine Article (R) Number: QF525. IMMUNOCOMPETENT CELLS OF THE UPPER AIRWAY - FUNCTIONS IN NORMAL AND DISEASED MUCOSA. BRANDTZAEG P (Reprint). UNIV OSLO, NATL HOSP, RIKSHOSP, INST PATHOL, IMMUNOHISTOCHEM & IMMUNOPATHOL LAB, N-0027 OSLO, NORWAY (Reprint). EUROPEAN ARCHIVES OF OTO-RHINO-LARYNGOLOGY (JAN 1995) Vol. 252, Supp. [1], pp. S8-S21. ISSN: 0937-4477. Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Secretory immunity is central in primary defense of the airway mucosa. B cells involved in this local immune system are initially stimulated in mucosa-associated lymphoid tissue, including tonsils and adenoids, and then migrate to secretory effector sites where they become immunoglobulin (Ig)-producing plasma cells. Locally produced Ig consists mainly of J-chain-containing dimers and larger polymers of IgA (pIgA) that are selectively transported through glandular cells by an epithelial receptor called secretory component or pIgR. Secretory antibodies perform surface protection by immune exclusion of soluble antigens as well as **infectious agents.** Ige can also participate in this primary defense because it reaches secretions by passive diffusion similar to IgE. However, the inflammatory properties of antibodies belonging to the latter two classes explain their involvement in mucosal immunopathology when elimination of penetrating antigens is unsuccessful. T helper (Th) cells activated in this process may by a Th2 profile of cytokines promote persistent inflammation with extravasation and priming of eosinophils. This mechanism appears to occur in the late-phase allergic reaction, perhaps driven mainly by interleukin-4 (IL-4) released

from mast cells subjected to IgE-mediated degranulation. Eosinophils are potentially tissue-destructive cells, particularly after priming with IL-5. Cytokines also up-regulate adhesion molecules on vascular endothelium and epithelium, thereby enhancing migration of eosinophils and other leukocytes into the mucosa. Intercellular adhesion molecule-1 (ICAM-1), which is readily up-regulated by interferon-gamma on airway epithelium, is of particular importance for further migration of leukocytes onto the mucosal surface. However, epithelial ICAM-1 may also provide a co-signal for overstimulation of CD4(+) T lymphocytes by antigen-presenting **HLA-DR**(+) epithelium. This latter occurrence could partly explain the airway mucosa appearing less able than gut mucosa to engage CD8(+) suppressor cells for down-regulation of hypersensitivity reactions against environmental antigens. Nevertheless, mucosal induction of immunological tolerance may be possible in the future. Therapeutic control of mucosal expression of adhesion molecules may likewise become an adjunct in the treatment of allergic disease.

L17 ANSWER 44 OF 59 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

95051524 EMBASE Document No.: 1995051524. Immunocompetent cells of the upper airway: Functions in normal and diseased mucosa. Brandtzaeg P.. Immunohistochem Immunopath (LIIPAT), Inst Pathology, University of Oslo, National Hospital, Rikshospitalet,N-0027 Oslo, Norway. European Archives of Oto-Rhino-Laryngology Vol. 252, No. SUPPL. 1, pp. S8-S21 1995. ISSN: 0937-4477. CODEN: EAOTE7

Pub. Country: Germany. Language: English. Summary Language: English.

ED Entered STN: 950301

AB Secretory immunity is central in primary defense of the airway mucosa. B cells involved in this local immune system are initially stimulated in mucosa-associated lymphoid tissue, including tonsils and adenoids, and then migrate to secretory effector sites where they become immunoglobulin (Ig)-producing plasma cells. Locally produced Ig consists mainly of J-chain-containing dimers and larger polymers of IgA (pIgA) that are selectively transported through glandular cells by an epithelial receptor called secretory component or pIgR. Secretory antibodies perform surface protection by immune exclusion of soluble antigens as well as **infectious agents.** IgG can also participate in this primary defense because it reaches secretions by passive diffusion similar to IgE. However, the inflammatory properties of antibodies belonging to the latter two classes explain their involvement in mucosal immunopathology when elimination of penetrating antigens is unsuccessful. T helper (Th) cells activated in this process may by a Th2 profile of cytokines promote persistent inflammation with extravasation and priming of eosinophils. This mechanism appears to occur in the late-phase allergic reaction, perhaps driven mainly by interleukin-4 (IL-4) released from mast cells subjected to IgE-mediated degranulation. Eosinophils are potentially tissue-destructive cells, particularly after priming with IL-5. Cytokines also up-regulate adhesion molecules on vascular endothelium and epithelium, thereby enhancing migration of eosinophils and other leukocytes into the mucosa. Intercellular adhesion molecule-1 (ICAM-1), which is readily up-regulated by interferon-γ on airway epithelium, is of particular importance for further migration of leukocytes onto the mucosal surface. However, epithelial ICAM-1 may also provide a co-signal for overstimulation of CD4+ T lymphocytes by antigen-presenting **HLA-DR**+ epithelium. This latter occurrence could partly explain the airway mucosa appearing less able than gut mucosa to engage CD8+ suppressor cells for down-regulation of hypersensitivity reactions against environmental antigens. Nevertheless, mucosal induction of immunological tolerance may be possible in the future. Therapeutic control of mucosal expression of adhesion molecules may likewise become an adjunct in the treatment of allergic disease.

L17 ANSWER 45 OF 59 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1994:759541 The Genuine Article (R) Number: PT349. ALTERATIONS IN THE MUCOSAL

IMMUNE-SYSTEM IN ULCERATIVE-COLITIS AND CROHNS-DISEASE. MACDERMOTT R P (Reprint). LAHEY CLIN FDN, GASTROENTEROL SECT, 41 MALL RD, BURLINGTON, MA 01805 (Reprint). MEDICAL CLINICS OF NORTH AMERICA (NOV 1994) Vol. 78, No. 6, pp. 1207-1231. ISSN: 0025-7125. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The intestinal lumen is normally populated with large numbers of bacteria, viral agents, and dietary antigens. Therefore, intestinal host defense mechanisms are critical to maintain mucosal integrity and depend, in large part, on regulatory processes mediated by the intestinal mucosal immune system. The mucosal immune system has unique protective functions and effector capabilities that normally do not lead to damage of the intestine. In healthy individuals, nutrients cross the interface between the external environment (the gut lumen) and the intestinal mucosa, while the crossing of potentially injurious agents must be prevented effectively and efficiently.(16, 90, 139) A central function of the normal intestinal immune system is the ability to recognize specifically and neutralize **infectious agents** as well as potentially injurious toxins or antigens.(48, 142) Discrimination between self and nonself is also critical, so that host tissues are not damaged during the time that host protective defense mechanisms are being employed.

An effective normal immune response begins with the specific processing of antigens by monocytes and macrophages, which endocytose large molecules and infectious organisms such as bacteria and viruses.(141) After lysosomal processing, smaller fragments are generated that interact with major histocompatibility complex (MHC) class II determinants. Antigen recognition events by lymphocytes involve the antigen-specific T cell receptor/CD2 complex. The T cell receptor complex specifically recognizes class II cell surface determinants in conjunction with antigen fragments on the macrophage surface. It is now clear that other cell types in addition to the macrophage have class II antigens on their surface and are capable of antigen presentation. The gastrointestinal tract, in particular, is populated by many potential antigen-presenting cells, including epithelial cells and endothelial cells as well as dendritic cells and macrophages. The presence of a variety of antigen-presenting cells further enhances the ability of the intestine to mount specific mucosal immune responses against the many different lumenal antigens to which it is exposed.(10, 11) Specific antigen recognition is pivotal to the normal function of T cells, which both regulate immune responses through T helper cell function and serve as effector cells by carrying out T cell-mediated cytotoxicity.

Cytokines, produced by macrophages(28) and T cells, induce B cells to mature into plasma cells and to secrete immunoglobulins. Presentation of antigens to B cells initiates an orderly, precise sequence of events during which genes that code for the variable regions are joined with genes that code for the constant regions of heavy and light chains of immunoglobulins. This sequence of events results in the formation of specific DNA, which produces a specific messenger RNA that, in turn, allows a B cell to secrete an isotope and subclass-defined antibody specific for the initiating antigen. The mucosal immune system has unique mechanisms that allow mucosal B cells to ''switch'' from predominantly IgM production to IgA production.(63, 64) A series of cell-mediated and cytokine-mediated regulatory events are involved in the production of IgA, which is the major mucosal protective immunoglobulin. Within normal human mucosal lymphoid follicles, T cell subsets produce specific B cell. switch, differentiation, and growth factors, which regulate IgA production by B cells.(21) T cell recognition functions are controlled by the formation of a T cell receptor complex with two polypeptide chains (alpha and beta), which have variable regions. Sensitized T cells recognize specific antigens in conjunction with MHC class II molecules. Helper T lymphocytes are then stimulated by interleukin-1 released from antigen-activated macrophages.(28) increased production of interleukin-2 by T cells further stimulates helper T cells to undergo cell cycle progression and clonal expansion.(130)

In ulcerative colitis (UC) and Crohn's disease (CD), the normally protective T and B cell immune response is not appropriately down-regulated, and highly activated effector cells produce prolonged, severe damage to the intestine. The immune system and inflammatory processes within the intestine thus exacerbate and perpetuate the intestinal injury in inflammatory bowel disease (IBD). Advances in understanding of normal immune and inflammatory processes in the intestinal mucosa have continued to provide new insights into the immunopathogenic mechanisms involved in chronic inflammatory intestinal diseases such as UC and CD.(79, 80) In this article, an overview and update of current concepts and progress in the role of the mucosal immune system in IBD are presented.

L17 ANSWER 46 OF 59 MEDLINE on STN DUPLICATE 15
95125345. PubMed ID: 7824838. How could **infectious agents** hide in synovial cells? Possible mechanisms of persistent viral infection in a model for the etiopathogenesis of chronic arthritis. Huppertz H I. (Children's University Hospital, Wurzburg, Germany.) Rheumatology international, (1994) 14 (2) 71-5. Journal code: 8206885. ISSN: 0172-8172. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB It has been hypothesized that a persistent intra-articular viral infection might play an important part in the pathogenesis of chronic arthritis. However, it remains unclear how such an infection could survive in synovial cells that express large amounts of **HLA-DR** and intercellular adhesion molecule-1 (ICAM-1) by which they communicate with immunocompetent cells. In an in vitro model of persistent mumps virus infection of synovial cells, results suggested that, in contrast to mock-infected cells, cells containing viral antigen did not express **HLA-DR** in response to interferon-gamma and that they did not up-regulate ICAM-1 expression under these conditions. Previously it has been shown that infected synovial cells do not express viral surface antigens. By these mechanisms, infected cells, interspersed among a large majority of uninfected cells, might evade recognition and eradication by the immune system. Lack of neoantigen expression on infected cells might be an important viral strategy to maintain a persistent infection and to initiate and perpetuate joint inflammation.

L17 ANSWER 47 OF 59 EMBASE
94251853 EMBASE Document No.: 1994251853. Infection and molecular mimicry in autoimmune diseases of childhood. Albani S.. Department of Pediatrics, University of California, 9500 Gilman Drive,San Diego, CA 92093-0663, United States. Clinical and Experimental Rheumatology Vol. 12, No. SUPPL. 10, pp. S35-S41 1994.
ISSN: 0392-856X. CODEN: CERHDP
Pub. Country: Italy. Language: English. Summary Language: English.

ED Entered STN: 940907

AB The etiopathogenesis of childhood chronic autoimmune disease is, in most cases, unknown. Most likely, several factors overlap in determining the loss of tolerance toward certain autoantigens that become the target of the disease and the main cause of its perpetuation. **Infectious agents** have often been implicated in the pathogenesis of these diseases, but, to date, compelling evidence for a horizontal transmission or for localized epidemics is lacking. Human pathogens may nevertheless play a role in determining the loss of tolerance toward certain self-antigens by means of mechanisms other than classic infection. It is common knowledge that human pathogens often express proteins with high antigenic potential with important homologies with human proteins. Evolutionary pressures based upon the necessity of escaping the host's specific immune responses may have determined this phenomenon, called 'molecular mimicry'. It is reasonable to assert that certain individuals can develop abnormal immune responses upon contact with an antigen that mimics a self-protein. These responses may ultimately lead to self-reactivity and autoimmune disease. In this model of molecular

mimicry, self-reactivity is triggered by cross-recognition of a self and an exogenous protein that bear the same sequence. A disease triggered by such a mechanism should present with: i) some form of an acute or chronic autoimmune clinical manifestation; ii) a documented clinical correlation between contact with a human pathogen and the autoimmune disease; iii) immune cross-reaction between a protein from a pathogen and a homologous human protein. Acute rheumatic fever, Reiter's syndrome and the other reactive arthritides fulfill the above conditions. Our hypothesis is that similar mechanisms may contribute to the pathogenesis of other autoimmune diseases in childhood. I will discuss herein our work on juvenile rheumatoid arthritis and juvenile dermatomyositis.

L17 ANSWER 48 OF 59 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

1992:733008 The Genuine Article (R) Number: KC389. IMMUNOHISTOCHEMICAL FINDINGS IN OTOSCLEROTIC LESIONS. ALTERMATT H J (Reprint); GERBER H A; GAENG D; MULLER C; ARNOLD W. UNIV BERN, INST PATHOL, MURTENSTR 31, CH-3010 BERN, SWITZERLAND (Reprint). HNO (DEC 1992) Vol. 40, No. 12, pp. 476-479. ISSN: 0017-6192. Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010. Language: German.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Despite numerous scientific efforts, the etiology of otosclerosis still remains unknown. Pathogenically, there are several signs of a chronic inflammatory process of the bony otic capsule. In this study, we tried to characterize the components of chronic inflammation by immunohistochemical techniques. Within otosclerotic lesions a mixed cellular infiltrate can be observed, consisting of lymphocytes, macrophages and plasma cells. Macrophages which are capable of presenting antigen in association with major histocompatibility antigens (MHC) class I and class II to CD8+-, and CD4+-T cells, respectively, were found in otosclerotic lesions based on their expression of the MAC387 antigen. Furthermore, **HLA-DR** positive cells and complement C3 have been found in resorption lacunae of otosclerotic lesions. Several osteoblasts and chondrocytes in active otosclerotic lesions reveal a strong surface expression of beta-2-microglobulin, indicating an increased MHC class I antigen expression in active otosclerotic lesions. In agreement with recently published data we found that a large fraction of the lymphoid cells are antigen-primed T-cells expressing an alpha/beta T-cell receptor in association with CD3 molecules on their surfaces. CD4+ lymphocytes which functionally represent lymphokine-secreting cells are activated through the specific recognition of antigen, presented in context with MHC class II molecules such as **HLA-DR.** Therefore, the presence of MHC class II positive cells arc crucial for the initiation of a local immune response. Thus, our observation of **HLA-DR** positive cells in olosclerotic lesions is of particular interest. Cells expressing the MHC class I associated protein beta-2-microglobulin are potential target cells for CD8+-T-lymphocytes which functionally mainly represent cytotoxic T lymphocytes that are also capable of secreting distinct lymphokines, such as interferon-gamma. In this context. the observed strong expression of beta-2-microglobulin by osteoblasts and chondrocytes may be of importance for the pathogenesis of otosclerotic lesions. The significance of these findings for an improved understanding of the etiology of otosclerosis remains open: since no material from very early otosclerotic lesions was available, we cannot conclusively state that an **infectious agent**, such as a virus infection, is the primary cause of the inflammatory response of the bone or that it truly represents an autoimmune disorder.

L17 ANSWER 49 OF 59 MEDLINE on STN DUPLICATE 16

91367016. PubMed ID: 1679864. Chronic fatigue syndrome: clinical condition associated with immune activation. Landay A L; Jessop C; Lennette E T; Levy J A. (Department of Immunology/Microbiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.) Lancet, (1991 Sep 21) 338 (8769) 707-12. Journal code: 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB There is much conflicting immunological and viral data about the causes of chronic fatigue syndrome (CFS); some findings support the notion that CFS may be due to one or more immune disorders that have resulted from exposure to an **infectious agent.** In the present study, flow cytometry and several different monoclonal antibodies recognising T, B, and natural killer (NK) cell populations as well as activation and cell adhesion antigens were used to study 147 individuals with CFS. Compared with healthy controls, a reduced CD8 suppressor cell population and increased activation markers (CD38, **HLA-DR**) on CD8 cells were found. The differences were significant ($p = 0.01$) in patient with major symptoms of the disease. These immunological indices were not observed in 80 healthy individuals, in 22 contacts of CFS patients, or in 43 patients with other diseases. No correlation of these findings in CFS patients with any known human viruses could be detected by serology. The findings suggest that immune activation is associated with many cases of CFS.

L17 ANSWER 50 OF 59 MEDLINE on STN
90226418. PubMed ID: 2328027. **Infectious agents**, immunity, and rheumatic diseases. Schwartz B D. (Howard Hughes Medical Institute, St. Louis, Missouri.) Arthritis and rheumatism, (1990 Apr) 33 (4) 457-65. Journal code: 0370605. ISSN: 0004-3591. Pub. country: United States. Language: English.

AB It should again be cautioned that these hypotheses are just that--hypotheses, for which there are some suggestive but not conclusive data. I have described these hypotheses using B27 and AS, and DR4 and RA. We are all aware that AS occurs in individuals who are B27 negative, and RA occurs in individuals who lack DR4. Although space does not permit further elaboration here, these hypotheses can be modified to take these additional associations into account. It should also be noted that even if the mechanisms advanced in these hypotheses prove to be true, different mechanisms may apply to different diseases, and several of these mechanisms may act in concert to produce disease. Nevertheless, these hypotheses provide a framework against which future experiments can be designed to further elucidate the relationship among **infectious agents**, immunity, and rheumatic diseases.

L17 ANSWER 51 OF 59 MEDLINE on STN DUPLICATE 17
91088000. PubMed ID: 2263315. Immunohistochemical characterization of the inflammatory infiltrate in amyotrophic lateral sclerosis. Troost D; Van den Oord J J; Vianney de Jong J M. (Department of Pathology, Academic Medical Centre, Amsterdam, The Netherlands.) Neuropathology and applied neurobiology, (1990 Oct) 16 (5) 401-10. Journal code: 7609829. ISSN: 0305-1846. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In order to test the hypothesis that the immune system plays a role in the pathogenesis of amyotrophic lateral sclerosis (ALS), the cellular composition of the spinal cord inflammatory infiltrate was analysed in eight cases of sporadic ALS by a panel of monoclonal antibodies. The majority of the many diffusely scattered lymphocytes seen in the anterior and lateral corticospinal tracts and anterior horns belonged to the suppressor/cytotoxicity T-cell subset and were admixed with variable numbers of macrophages. Helper-inducer T-cells were rare and B-cells were conspicuously absent. Compared to controls, ALS specimens exhibited an increase in major histocompatibility complex (MHC) products or human leucocyte antigens (HLA) in the corticospinal tracts and anterior horns. HLA-ABC antigens were expressed in the honeycomb pattern of the glial matrix of the spinal cord, and **HLA-DR** antigens were strongly expressed by large dendritic cells. In addition, macrophages and endothelial cells were labelled by **HLA-DR.** These findings suggest that an autoimmune process or **infectious agent** may play a role in ALS.

L17 ANSWER 52 OF 59 MEDLINE on STN
89312579. PubMed ID: 2664347. HLA class II polymorphism: implications for genetic susceptibility to autoimmune disease. Gregersen P K. (Department

of Medicine, North Shore University Hospital, Cornell University Medical College, Manhasset, New York 11030.) Laboratory investigation; a journal of technical methods and pathology, (1989 Jul) 61 (1) 5-19. Ref: 97. Journal code: 0376617. ISSN: 0023-6837. Pub. country: United States. Language: English.

AB Our understanding of HLA class II polymorphism has undergone a rapid evolution in the last few years. As in so many areas of modern biology, this progress has depended largely on the application of recombinant DNA techniques to the study of this gene family. In particular, the recent development of methods of gene amplification by means of the polymerase chain reaction has allowed for the rapid assessment of polymorphism in the human population. In addition, the elucidation by x-ray crystallographic analysis of the three-dimensional structure of an HLA molecule has been a major step. These areas of progress have now begun to converge to allow a more detailed approach to the problem of class II polymorphism and disease susceptibility. As discussed in this review, the data so far indicate that a few amino acid substitutions in class II molecules may exert a critical influence on susceptibility to autoimmune diseases such as RA and IDDM. The mechanism by which these class II polymorphisms predispose to autoimmune disease is still unknown. It is tempting to speculate that differences in the binding affinity of HLA molecules for autoantigens might be involved; however, as yet no specific autoantigen has been identified for either RA or IDDM. Intriguingly, sequence similarities have been observed between some viral proteins and class II molecules, raising the possibility that these **infectious agents** might induce autoimmunity by "molecular mimicry." Examples include the human cytomegalovirus protein, IE2 as well as the Epstein Barr virus gp110 protein. Other possible mechanisms involve more complex immunoregulatory effects, such as the absence of suppressor functions that appear to be under the influence of the HLA genes. To some extent, the persistent ignorance about the cause of autoimmunity reflects a general lack of knowledge concerning exactly how HLA polymorphisms exert immunoregulatory effects. For example, in addition to influencing antigen presentation, MHC molecules also affect the overall T cell repertoire during thymic selection. The relative importance of HLA class II polymorphism in exerting immunoregulatory effects by means of thymic selection of the T cell repertoire is unknown. For autoimmune diseases such as RA and IDDM, there is a need to identify a specific functional abnormality that is causing the disease before the etiological significance of the emerging associations with class II polymorphisms become clear. (ABSTRACT TRUNCATED AT 400 WORDS)

L17 ANSWER 53 OF 59 MEDLINE on STN

89374567. PubMed ID: 2978456. Diminished interferon gamma production may be the earliest indicator of infection with the human immunodeficiency virus. Cauda R; Tyring S K; Tamburrini E; Ventura G; Tambarello M; Ortona L. (Department of Infectious Diseases, Catholic University, Rome, Italy.) Viral immunology, (1987-88) 1 (4) 247-58. Journal code: 8801552. ISSN: 0882-8245. Pub. country: United States. Language: English.

AB The degree of clinical severity in human immunodeficiency virus infected patients, ranging from asymptomatic seropositive subjects to acquired immune deficiency syndrome, as well as in individuals at risk was assessed in relation to: (1) T-cell subset balance and expression of markers of T-cell activation; (2) natural killer activity; and (3) interferon gamma production. A decrease in the CD4/CD8 (helper/suppressor) ratio and an increase in the percentage of CD8+ (suppressor/cytotoxic) cells coexpressing markers of activation (**HLA-DR** or CD25) were closely correlated with the clinical severity of the human immunodeficiency virus infection. Natural killer activity was significantly impaired in patients with acquired immune deficiency syndrome and acquired immune deficiency syndrome-related complex but normal in asymptomatic seropositive individuals and subjects at risk. Interferon gamma production, either in response to mitogens or the antigens from **infectious agents** commonly affecting human immunodeficiency virus-positive individuals, was decreased in

patients with acquired immune deficiency syndrome or acquired immune deficiency syndrome-related complex, with lesser involvement in human immunodeficiency virus-seropositive subjects or individuals at risk. Four of the six persons in the last group seroconverted during the ten months subsequent to evaluation of their immune status. Since production of interferon gamma was diminished in these patients while other assays of immunity were normal, measurement of this lymphokine may be a useful determinant of infection with the human immunodeficiency virus.

L17 ANSWER 54 OF 59 MEDLINE on STN DUPLICATE 18
87199126. PubMed ID: 3494857. Serologic and immunologic studies in patients with AIDS in North America and Africa. The potential role of **infectious agents** as cofactors in human immunodeficiency virus infection. Quinn T C; Piot P; McCormick J B; Feinsod F M; Taelman H; Kapita B; Stevens W; Fauci A S. JAMA : journal of the American Medical Association, (1987 May 15) 257 (19) 2617-21. Journal code: 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.
AB Serologic and immunologic studies were performed in 38 African and 60 US patients with acquired immunodeficiency syndrome (AIDS), 100 African and 100 US heterosexual men and women, and 100 US homosexual men to examine the potential role of **infectious agents** in human immunodeficiency virus (HIV) infection. There were no significant differences in the prevalence of antibodies to cytomegalovirus, Epstein-Barr virus, hepatitis A and B viruses, herpes simplex virus, syphilis, and toxoplasmosis among the African and US patients with AIDS, African heterosexual controls, and US homosexual men. However, these four groups all demonstrated a significantly greater prevalence of antibodies to each of these **infectious agents** compared with US heterosexual men. Immunologic studies demonstrated a significant elevation of activated lymphocytes (**HLA-DR** and T3 positive) and immune complexes in both AIDS populations and African heterosexual and US homosexual populations, compared with the US heterosexual population. These data demonstrate that the immune systems of African heterosexuals, similar to those of US homosexual men, are in a chronically activated state associated with chronic viral and parasitic antigenic exposure, which may cause them to be particularly susceptible to HIV infection or disease progression.

L17 ANSWER 55 OF 59 MEDLINE on STN
88035067. PubMed ID: 2959756. Factors influencing circulating OKT8 cell phenotypes in patients with multiple sclerosis. Hughes P J; Kirk P F; Dyas J; Munro J A; Welsh K I; Compston D A. (Department of Neurology, University of Wales College of Medicine, Cardiff, UK.) Journal of neurology, neurosurgery, and psychiatry, (1987 Sep) 50 (9) 1156-9. Journal code: 2985191R. ISSN: 0022-3050. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Peripheral blood OKT8 cell phenotypes were correlated with measurements of plasma cortisol and serological evidence for exposure to 15 **infectious agents**, in longitudinal studies involving 13 patients with multiple sclerosis, 13 of their siblings, nine spouses and 13 unrelated controls; 44/48 individuals were HLA typed. Neither circadian rhythms, nor exposure to any one **infectious agent** accounted for the serial changes in OKT8 cells but there was an association between the presence of HLA-DR2 and periodic reductions in OKT8 cells irrespective of clinical status. Taken with previously reported serial observations in patients and cohabiting relatives, this finding provides indirect evidence for an interplay between environmental and genetic factors in determining OKT8 cell phenotypes in multiple sclerosis.

L17 ANSWER 56 OF 59 MEDLINE on STN DUPLICATE 19
88146824. PubMed ID: 3439184. [Value and indications for bronchoalveolar lavage combined with transbronchial lung biopsy]. Aussage- und Einsatzmoglichkeiten der bronchioloalveolaren Lavage kombiniert mit transbronchialer Lungenbiopsie. Popper H; Pongratz M. (Laboratorium fur

Umwelt- und Atemtraktpathologie, Institut fur Pathologische Anatomie, Universitat Graz.) Wiener klinische Wochenschrift, (1987 Dec 18) 99 (24) 848-55. Journal code: 21620870R. ISSN: 0043-5325. Pub. country: Austria. Language: German.

AB Bronchioloalveolar lavage (BAL) enables diffuse interstitial lung disease to be divided into lymphocytic and granulocytic alveolitis. The combination of BAL and transbronchial lung biopsies using modern flexible fiberoptic bronchoscopes allows the subdivision of lymphocytic alveolitis into sarcoidosis, exogenic allergic alveolitis (synonym: hypersensitivity pneumonitis: EAA) and granulomatous pneumonias caused by **infectious agents.** The use of immunohistochemical surface markers of lymphocytes in conjunction with BAL provides further differentiation of lymphocytes into T- and B-, T-helper and T-suppressor types, natural killer cells (NK cells) and cytotoxic T-cells. A predominance of T-suppressor lymphocytes is an indication of EAA, whereas a predominance of T-helper lymphocytes is positively correlated with sarcoidosis. Other markers, e.g. **HLA-DR**, when expressed on the surface of alveolar macrophages, merely indicate activation unrelated to a specific type of lymphocytic alveolitis. BAL is also a new and promising diagnostic tool for pneumoconioses and other types of lung disease caused by inhaled industrial pollutants. Ferruginous bodies and silica crystals, free or ingested by alveolar macrophages, can be found more easily than by scraping tissue blocks or from multiple sections of transbronchial biopsies. BAL cells can easily be processed for electron microscopy and inhaled foreign material can be analysed in an electron microscope using X-ray diffraction analysis (EDAX) or electron spectroscopic imaging (ESI). BAL is also of value in the diagnosis of peripheral lung carcinomas, in addition to cytological sputum analysis, brush smears, transthoracic fine needle aspiration and transbronchial biopsies. BAL is a valuable diagnostic tool in cases of unusual pneumonia where fungi can be visualized by silver impregnation techniques and viruses by antibodies using immunofluorescence microscopy.

L17 ANSWER 57 OF 59 EMBASE DUPLICATE 20

88180918 EMBASE Document No.: 1988180918. Diminished interferon gamma production may be the earliest indicator of infection with the human immunodeficiency virus. Cauda R.; Tyring S.K.; Tamburrini E.; Ventura G.; Tambarello M.; Ortona L.. Department of Infectious Diseases, Catholic University, Rome, Italy. Viral Immunology Vol. 1, No. 4, pp. 247-258 1987.
ISSN: 0882-8245. CODEN: VIIMET
Pub. Country: United States. Language: English. Summary Language: English.

ED Entered STN: 911211

AB The degree of clinical severity in human immunodeficiency virus infected patients, ranging from asymptomatic seropositive subjects to acquired immune deficiency syndrome, as well as in individuals at risk was assessed in relation to: (1) T-cell subset balance and expression of markers of T-cell activation; (2) natural killer activity; and (3) interferon gamma production. A decrease in the CD4/CD8 (helper/suppressor) ratio and an increase in the percentage of CD8+ (suppressor/cytotoxic) cells coexpressing markers of activation (**HLA-DR** or CD25) were closely correlated with the clinical severity of the human immunodeficiency virus infection. Natural killer activity was significantly impaired in patients with acquired immune deficiency syndrome and acquired immune deficiency syndrome-related complex but normal in asymptomatic seropositive individuals and subjects at risk. Interferon gamma production, either in response to mitogens or the antigens from **infectious agents** commonly affecting human immunodeficiency virus-positive individuals, was decreased in patients with acquired immune deficiency syndrome or acquired immune deficiency syndrome-related complex, with lesser involvement in human immunodeficiency virus-seropositive subjects or individuals at risk. Four of the six persons in the last group seroconverted during the ten months subsequent to evaluation of their immune status. Since production of

interferon gamma was diminished in these patients while other assays of immunity were normal, measurement of this lymphokine may be a useful determinant of infection with the human immunodeficiency virus.

L17 ANSWER 58 OF 59 MEDLINE on STN
88062655. PubMed ID: 3681949. Class II MHC antigen (HLA-DR3) predisposes to sarcoid arthritis. Krause A; Goebel K M. (Department of Medicine, University Hospital, Marburg, West Germany.) Journal of clinical & laboratory immunology, (1987 Sep) 24 (1) 25-7. Journal code: 7808987. ISSN: 0141-2760. Pub. country: Italy. Language: English.
AB Recent studies indicate that the susceptibility to various inflammatory rheumatic diseases is an inherited trait determined by gene products of the class II histocompatibility complex (**HLA-DR** determinants). In a study designed to evaluate the concept of inherited susceptibility to sarcoid arthritis (SA), 42 patients with histologically proved acute disease underwent typing of HLA-A, -B, -C and -DR antigens. Using the microdroplet assay of human serum cytotoxins, we employed 156 antiserums to identify 52 antigens on A, B and C loci and 35 to identify 7 DR antigens on the surface of B cells. An ethnically matched control group consisted of 134 healthy volunteers. The frequency of B cell isoantigen DR3 specificity was significantly increased in patients with SA (relative risk, 4.8); HLA-DR3 was found in 25 (60%) of the patients, compared with 31 (23%) of the controls. This study lends further support to the hypothesis that the putative role of an **infectious agent** triggering SA cannot be judged without considering genetic cofactors.

L17 ANSWER 59 OF 59 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
1983:162170 Document No.: PREV198375012170; BA75:12170. DISSEMINATED KAPOSIS SARCOMA IN HOMO SEXUAL MEN. FRIEDMANN-KIEN A E [Reprint author]; LAUBENSTEIN L J; RUBINSTEIN P; BUIMOVICI-KLEIN E; MARMOR M; STAHL R; SPIGLAND I; KIM K S; ZOLLA-PAZNER S. NEW YORK UNIV MED CENT, 530 FIRST AVE, NEW YORK, NY 10016, USA. Annals of Internal Medicine, (1982) Vol. 96, No. 6 PART 1, pp. 693-700.
CODEN: AIMEAS. ISSN: 0003-4819. Language: ENGLISH.
AB Nineteen cases from an epidemic of disseminated Kaposi's sarcoma in homosexual men were studied by clinical, virologic, immunologic and genetic methods. The patients were all male homosexuals ranging in age from 29 to 52 yr, with histories of multiple sexually transmitted diseases and exposure to prescription and recreational drugs. Sites of disease included skin (16 of 19 patients), lymph nodes (13 patients), gastrointestinal tract (12 patients), spleen (3 patients), and lung (1 patient). Most patients had elevated levels of serum Ig, positive antibody titers to hepatitis A and B virus, cytomegalovirus and Epstein-Barr virus, and impairment of cell-mediated immunologic reactions. The frequency of HLA-DR5 in these patients was significantly elevated. Two of the 19 patients died. Although the precise cause of this epidemic is unknown, it is likely that a genetic predisposition, an acquired immunoregulatory defect, and 1 or more **infectious agents** and drugs may be involved.

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L22         22 L21 AND HLA

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L23           6 DUP REMOVE L22 (16 DUPLICATES REMOVED)
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L23 ANSWER 1 OF 6 MEDLINE on STN DUPLICATE 1
2005092527. PubMed ID: 15721390. Lymphoid tissue **targeting** of anti-HIV drugs using liposomes. **Desormeaux Andre**; **Bergeron Michel G.** (Centre de Recherche en Infectiologie, Centre Hospitalier Universitaire de Quebec, Quebec, Canada.) Methods in enzymology, (2005) 391 330-51. Journal code: 0212271. ISSN: 0076-6879. Pub. country: United States. Language: English.

AB Considering that HIV-1 accumulates and replicates actively within lymphoid tissues, any strategy that will decrease viral stores in these tissues might be beneficial to the infected host. Follicular dendritic cells (FDC), B lymphocytes, antigen-presenting cells like macrophages, and activated CD4(+) T cells are abundant in lymphoid tissues, and all express substantial levels of the **HLA**-DR determinant of the major histocompatibility complex class II (MHC-II). Monocyte-derived macrophages, which are also CD4(+) and express **HLA**-DR, are considered to be the most frequent hosts of HIV-1 in tissues of infected individuals. This chapter describes a method for the generation of sterically stabilized immunoliposomes grafted with anti-**HLA**-DR antibodies that allows efficient delivery of drugs to lymphoid tissues. The method first involves the production of murine **HLA**-DR (clone Y-17, IgG(2b)) and human **HLA**-DR (clone 2.06, IgG(1)) antibodies from hybridomas in mice and their purification from ascites fluids. This step is followed by the production of Fab' fragments of antibodies 2.06 and Y-17 that are grafted at the surface of sterically stabilized immunoliposomes instead of the complete IgG to reduce their immunogenicity. The preparation of sterically stabilized liposomes, the composition of which allows an efficient entrapment and retention of several drugs, by the method of thin lipid film hydratation followed by extrusion through polycarbonate membranes is then described. This step is followed by the removal of unencapsulated drug, when present, by low-speed centrifugation of the liposomal preparation through a Sephadex G-50 column. These liposomes contain a fixed amount of poly(ethylene glycol) chain terminated by a maleimide reactive group for the coupling of Fab' fragments. The procedure for the coupling of Fab' fragments at the surface of sterically stabilized liposomes and the removal of uncoupled fragments of antibodies is described. In vitro binding studies of sterically stabilized immunoliposomes to cell lines expressing different surface levels of the mouse or human **HLA**-DR determinant of MHC-II demonstrate that these liposomes are very specific. When compared with conventional liposomes, the subcutaneous administration in the upper back, below the neck, of mice of anti-**HLA**-DR immunoliposomes resulted in a 2.9 and 1.6 times greater accumulation in the cervical and brachial lymph nodes, respectively. The use of sterically stabilized immunoliposomes increases 2 to 4.6 times the concentration of liposomes in all tissues, with a peak accumulation at 240 h in brachial, inguinal, and popliteal lymph nodes and at 360 h or greater in cervical lymph nodes. A single bolus injection of indinavir given subcutaneously to mice results in no significant drug levels in lymphoid organs. Most of the injected drug accumulates in the liver and is totally cleared within 24 h postadministration. In contrast, sterically stabilized immunoliposomes are very efficient in delivering high concentrations of indinavir to lymphoid tissues for at least 15 days postinjection. The drug accumulation in all tissues leads to a 21- to 126-fold increased accumulation when compared with the free agent. Anti-**HLA**-DR immunoliposomes containing indinavir are as efficient as the free agent in inhibiting HIV-1 replication in PM1 cells that express high levels of cell surface **HLA**-DR. Sterically stabilized anti-**HLA**-DR immunoliposomes mostly accumulate in the cortex in which follicles (B cells and FDCs) are located, and in parafollicular areas in which T cells, interdigitating dendritic cells, and other accessory cells are abundant. The delivery of drugs in this area of the lymph nodes could represent a convenient strategy to inhibit more efficiently HIV-1 replication.

Although the method described in this chapter is specific to the coupling of anti-**HLA**-DR antibodies, any antibody fragment or peptide specific for an antigen present in relatively large quantities at the surface of lymphoid cells, that is anchored to the surface of sterically stabilized liposomes with an appropriate coupling method, can be used to concentrate drugs within target tissues and improve the therapeutic effect of drugs.

L23 ANSWER 2 OF 6 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2002034261 EMBASE Targeted delivery of indinavir to HIV-1 primary reservoirs with immunoliposomes. Gagne J.-F.; **Desormeaux A.**; Perron S.; **Tremblay M.J.**; **Bergeron M.G.**. M.G. Bergeron, Centre de Recherche en Infectiologie, Centre Hospitalier Univ. de Quebec, Universite Laval, 2705 Blvd Laurier, Quebec, Que., Canada. michel.g.bergeron@crchul.ulaval.ca. Biochimica et Biophysica Acta - Biomembranes Vol. 1558, No. 2, pp. 198-210 1 Feb 2002. Refs: 44.
ISSN: 0005-2736. CODEN: BBBMBS
S 0005-2736(01)00432-1. Pub. Country: Netherlands. Language: English. Summary Language: English.

ED Entered STN: 20020207

AB The tissue distribution of indinavir, free or incorporated into sterically stabilized anti-**HLA**-DR immunoliposomes, has been evaluated after a single subcutaneous injection to C3H mice. Administration of free indinavir resulted in low drug levels in lymphoid organs. In contrast, sterically stabilized anti-**HLA**-DR immunoliposomes were very efficient in delivering high concentrations of indinavir to lymphoid tissues for at least 15 days post-injection increasing by up to 126 times the drug accumulation in lymph nodes. The efficacy of free and immunoliposomal indinavir has been evaluated in vitro. Results showed that immunoliposomal indinavir was as efficient as the free agent to inhibit HIV-1 replication in cultured cells. The toxicity and immunogenicity of repeated administrations of liposomal formulations have also been investigated in rodents. No significant differences in the levels of hepatic enzymes of mice treated with free or liposomal indinavir were observed when compared to baseline and control untreated mice. Furthermore, histopathological studies revealed no significant damage to liver and spleen when compared to the control group. Liposomes bearing Fab' fragments were 2.3-fold less immunogenic than liposomes bearing the entire IgG. Incorporation of antiviral agents into sterically stabilized immunoliposomes could represent a novel therapeutic strategy to target specifically HIV reservoirs and treat more efficiently this retroviral infection. .COPYRGT. 2002 Elsevier Science B.V. All rights reserved.

L23 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

2000:790356 Document No. 133:340273 Methods and formulations for **targeting** infectious agents bearing host cell proteins. **Bergeron, Michel G.; Desormeaux, Andre; Tremblay, Michel J.** (Infectio Recherche Inc., Can.). PCT Int. Appl. WO 2000066173 A2 20001109, 45 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-CA469 20000503. PRIORITY: CA 1999-2270600 19990503.

AB A formulation is disclosed for the treatment of diseases caused by an infectious agent which acquires host membranes protein during its life cycle. The formulation is a **targeting** pharmaceutical composition It comprises a ligand capable of binding the host membrane proteins coupled to a lipid-comprising vesicle, which may comprise or not a drug effective in the treatment of the disease. Specific liposomes bearing anti-

HLA-DR or anti-CD4 antibodies comprising or not antiviral drugs, namely anti-HIV drugs, are disclosed and claimed. A method of formulation as well as a method of using the formulation in the treatment of a disease are also disclosed.

L23 ANSWER 4 OF 6 MEDLINE on STN DUPLICATE 3

2001338262. PubMed ID: 11101055. **Targeting** cell-free HIV and virally-infected cells with anti-**HLA**-DR immunoliposomes containing amphotericin B: Bestman-Smith J; **Desormeaux A; Tremblay M J; Bergeron M G.** (Centre de Recherche en Infectiologie, Centre Hospitalier Universitaire de Quebec, Canada.) AIDS (London, England), (2000 Nov 10) 14 (16) 2457-65. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To evaluate the ability of liposomes bearing anti-**HLA** -DR Fab' fragments (immunoliposomes) and containing amphotericin B (AmB) to target and neutralize cell-free HIV-1 particles and virally-infected cells. METHODS: The effect of AmB on the attachment and fusion of HIV-1(NL4-3) to Jurkat E6.1 cells has been evaluated using a p24 enzymatic assay. The ability of AmB to inhibit HIV-1-based luciferase reporter viruses pseudotyped with HXB2, AML-V and VSV-G envelopes has been evaluated in Jurkat E6.1 cells. The efficacy of free and immunoliposomal AmB to inhibit cell-free HIV, that have incorporated or not **HLA** -DR molecules, has been evaluated in **HLA**-DR/negative (NEG) 1G5 T cells and **HLA**-DR/positive (POS) Mono Mac 1 cells. RESULTS: AmB inhibited HIV infectivity independently of the nature of viral envelope proteins. Pretreatment of HIV with AmB had no major effect on viral attachment and fusion process to Jurkat E6.1 cells. Immunoliposomal AmB (0.5 microg/ml) led to a 77% inhibition of replication of **HLA** -DR/POS HIV-1 with no cell toxicity, whereas free AmB had no significant antiviral activity at this concentration. A complete inhibition of viral replication was observed following incubation of viruses with immunoliposomal AmB (2.5 microg/ml). Anti-**HLA**-DR immunoliposomes containing AmB had no effect on the infectivity of **HLA**-DR/NEG HIV-1 particles in **HLA**-DR/NEG T lymphoid cells but completely inhibited replication of viruses in an **HLA** -DR/POS monocytic cell line. CONCLUSION: The incorporation of neutralizing agents in anti-**HLA**-DR immunoliposomes could represent a novel therapeutic strategy to specifically target cell-free HIV particles and virally-infected cells to treat HIV infection more efficiently.

L23 ANSWER 5 OF 6 MEDLINE on STN DUPLICATE 4

2001048034. PubMed ID: 11018661. Sterically stabilized liposomes bearing anti-**HLA**-DR antibodies for **targeting** the primary cellular reservoirs of HIV-1. Bestman-Smith J; Gourde P; **Desormeaux A; Tremblay M J; Bergeron M G.** (Centre de Recherche en Infectiologie, Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, 2705 Blvd Laurier, G1V 4G2, Quebec, QC, Canada.) Biochimica et biophysica acta, (2000 Sep 29) 1468 (1-2) 161-74. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB The ability of liposomes bearing anti-**HLA**-DR Fab' fragments at the end termini of polyethyleneglycol chains (sterically stabilized immunoliposomes) to target **HLA**-DR expressing cells and increase the accumulation of liposomes into lymphoid organs has been evaluated and compared to that of conventional liposomes, sterically stabilized liposomes and conventional immunoliposomes after a single subcutaneous injection to mice. The accumulation of sterically stabilized liposomes in lymph nodes was higher than that of conventional liposomes. Sterically stabilized immunoliposomes accumulated much better than conventional immunoliposomes in all tissues indicating that the presence of PEG has an important effect on the uptake of immunoliposomes by the lymphatic system. Fluorescence microscopy studies showed that sterically stabilized liposomes are mainly localized in macrophage-rich areas such as the subcapsular region of lymph nodes and in the red pulp and marginal zone of

the spleen. In contrast, sterically stabilized immunoliposomes mostly accumulated in the cortex in which follicles are located and in the white pulp of the spleen. As the human **HLA**-DR determinant of the major histocompatibility complex class II is expressed on activated CD4+ T lymphocytes and antigen presenting cells such as monocyte/macrophages and dendritic cells, known as the cellular reservoirs of HIV-1, liposomes bearing anti-**HLA**-DR antibodies constitute an attractive approach to concentrate drugs in HIV-1 reservoirs and improve their therapeutic effect.

L23 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 5
2000001973. PubMed ID: 10518698. **Targeting** lymph nodes with liposomes bearing anti-**HLA**-DR Fab' fragments. Dufresne I; **Desormeaux A**; Bestman-Smith J; Gourde P; **Tremblay M J**; **Bergeron M G.** (Centre de Recherche en Infectiologie, Universite Laval, Centre Hospitalier Universitaire de Quebec, Pavillon CHUL, 2705 Blvd. Laurier, Quebec, QC, Canada.) Biochimica et biophysica acta, (1999 Oct 15) 1421 (2) 284-94. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB The ability of liposomes bearing anti-**HLA**-DR Fab' fragments to target cells expressing the human **HLA**-DR determinant of the major histocompatibility complex class II (MHC-II) has been evaluated and compared to that of conventional liposomes. Anti-**HLA**-DR immunoliposomes did not bind to **HLA**-DR-negative cells. In contrast, a high level of binding was observed following incubation of immunoliposomes with cells bearing important levels of human **HLA** -DR. The accumulation of conventional and murine anti-**HLA**-DR immunoliposomes in different tissues has been investigated following a single subcutaneous injection given in the upper back of C3H mice. Anti-**HLA**-DR immunoliposomes resulted in a much better accumulation in the cervical and brachial lymph nodes when compared to conventional liposomes. The accumulation in the liver was similar for both liposomal preparations, whereas an approximately twofold decrease in accumulation was observed for immunoliposomes in the spleen. Given that **HLA** -DR surface marker is expressed on monocyte/macrophages and activated CD4+ T lymphocytes, the primary cellular reservoirs of the human immunodeficiency virus (HIV), the use of liposomes bearing surface-attached anti-**HLA**-DR could constitute a convenient strategy to more efficiently treat this debilitating retroviral disease. Moreover, the reported incorporation of high amounts of host-encoded **HLA**-DR proteins by HIV particles renders the use of liposomes bearing anti-**HLA**-DR antibodies even more attractive.

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FULL ESTIMATED COST	228.96	229.17

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-10.22	-10.22

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☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	(HLA-DR)same (antibod?)same (conjugated)same (liposome)	YES	OR	L7
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L1 and targeting	YES	OR	L8
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☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L9 and CD4	YES	OR	L10
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L10 and macrophage	YES	OR	L11
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L11 and conjugate	YES	OR	L12
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L12 and conjugated liposome	YES	OR	L13
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L12 and (HLA)adj (DR)	YES	OR	L14
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☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L15 and anti-HLA-DR	YES	OR	L16
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L15 and anti-HLADR	YES	OR	L17
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	(conjugated)adj (liposome)	YES	OR	L18
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L18 and anti-HLA	YES	OR	L19
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L18 and anti-HLA-DR	YES	OR	L20
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L18 and infectious	YES	OR	L21
☑	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	L21 and HLA-DR	YES	OR	L22
☑	USPT	5773027.pn.	YES	OR	L23

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